(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 283 310 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **26.05.93**

(51) Int. Cl.5: **C07D 295/04**, C07D 295/18, C07D 241/04, C07D 241/08, C07D 243/08, C07D 401/02, C07D 403/02, C07D 405/12, C07D 209/44, C07D 207/34, C07D 213/75

(21) Application number: **88302414.3**

(22) Date of filing: **18.03.88**

(54) N-Benzhydryl-substituted heterocyclic derivatives, their preparation and their use.

(30) Priority: **18.03.87 JP 63157/87**

(43) Date of publication of application:
21.09.88 Bulletin 88/38

(45) Publication of the grant of the patent:
26.05.93 Bulletin 93/21

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 126 449
DE-A- 2 024 350
GB-A- 1 434 580
US-A- 3 244 718
US-A- 3 652 568

CHEMICAL ABSTRACTS, vol. 64, no. 6, March 14, 1966, Columbus, Ohio, USA; UCB: "N-benzhydrylpiperazine derivatives", page 8207, abstract-no. 8 207f

(73) Proprietor: **Sankyo Company Limited**
5-1 Nihonbashi Honcho 3-chome Chuo-ku
Tokyo(JP)

(72) Inventor: **Hirai, Koichi c/o Sankyo Company Limited**
2-58, Hiromachi 1-chome
Shinagawa-ku Tokyo(JP)
Inventor: **Fujimoto, Katsumi c/o Sankyo Company Limited**
2-58, Hiromachi 1-chome
Shinagawa-ku Tokyo(JP)
Inventor: **Iwano, Yuji c/o Sankyo Company Limited**
2-58, Hiromachi 1-chome
Shinagawa-ku Tokyo(JP)
Inventor: **Matsui, Yoshiki c/o Sankyo Company Limited**
2-58, Hiromachi 1-chome
Shinagawa-ku Tokyo(JP)

EP 0 283 310 B1

CHEMICAL ABSTRACTS, vol. 88, no. 7, February 13, 1978, Columbus, Ohio, USA; J. VANDENBERK: "Piperazine and piperidine derivatives", page 555, abstract-no. 50 920n

CHEMICAL ABSTRACTS, vol. 71. no. 21, November 24, 1969, Columbus, Ohio, USA; D.J. VADODARIA: "Synthesis and central nervous system depressant activity of new piperazine derivatives and related compounds", page 348, abstract-no.101 817t

CHEMICAL ABSTRACTS, vol. 68, no. 19, May 6, 1968, Columbus, Ohio, USA; H.B. WRIGHT et al.: "Hypocholesteremic agents. IV. Some substituted piperazines", page 8277, abstract-no. 86 028d

(74) Representative: Gibson, Christian John Robert et al
MARKS & CLERK 57/60 Lincoln's Inn Fields
London WC2A 3LS (GB)

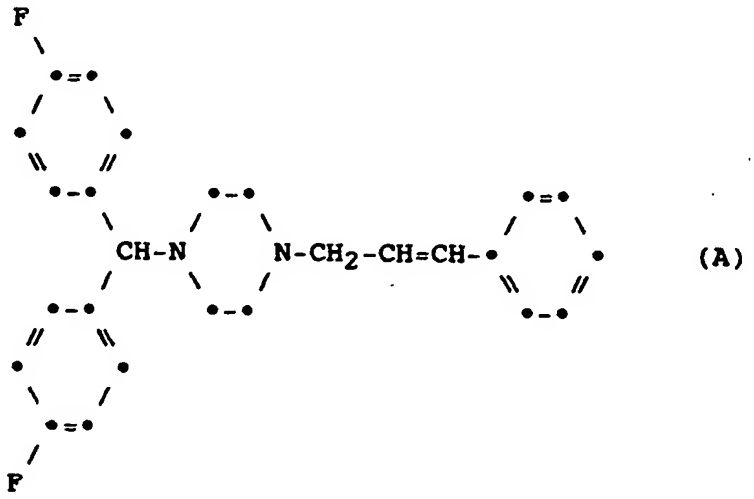
Description

The present invention relates to a series of novel heterocyclic compounds having a saturated heterocyclic ring containing two ring nitrogen atoms, one of which is substituted by a halobenzhydryl group and the other of which is substituted by certain specific substituted alkyl groups. The invention also provides a pharmaceutical composition for the treatment, inter alia, of disorders affecting circulation within the brain, and also provides processes for preparing the compounds of the present invention.

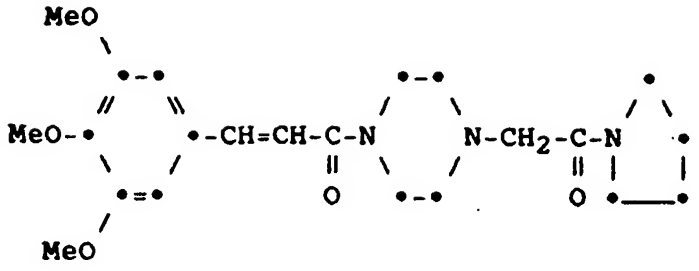
Maintenance of a good blood circulation is absolutely vital to continued good health in humans and other animals, and many compounds, of the class known generally as "vasodilators", have been used or proposed to be used to assist the circulation of the blood and/or to relieve symptoms arising from poor circulation. However, one of the most damaging and distressing consequences of circulatory problems is damage to the brain, which may be non-fatal but irreversible and can have serious effects on the personality and behaviour of the patient. Similar problems may also arise from other ischaemic events, which may or may not be the consequence of circulatory disorders. Unfortunately, relatively few of the many vasodilators available are indicated for use in the treatment of cerebral vascular insufficiency.

In accordance with the present invention, we have now discovered a series of new compounds which have shown exciting possibilities for the treatment of cerebral vascular disorders. The new compounds of the invention are characterized by a saturated heterocyclic ring containing two ring nitrogen atoms (e.g. an imidazolidine, piperazine or homopiperazine ring), one of the nitrogen atoms having a halobenzhydryl substituent and the other having a substituent comprising an alkyl group, itself having certain specific substituents thereon.

Of the several compounds which have been proposed for use in the treatment and prophylaxis of cerebral vascular disorders, the two compounds which most closely resemble those of the present invention, in terms both of molecular structure and pharmacological effects, are flunarizine (which itself was developed from the closely related drug cinnarizine) and cinepazide. Flunarizine and cinepazide are described in The Merck Index, Tenth Edition, published by Merck & Co. Inc., 1983, in monographs 4045 and 2267 respectively. These compounds are included amongst the compounds covered by United Kingdom Patents No. 1 268 710 and 1 218 591, respectively. Flunarizine has the formula (A) given below, whilst cinepazide has the formula (B):



(A)



(B)

In the above formulae, Me represents the methyl group.

These compounds are known to be calcium-entry blockers, i.e. they block or reduce the entry of calcium (as Ca^{2+}) into cells of the animal body. Calcium build-up in vulnerable brain cells has been shown to have a significant correlation with irreversible cell damage, and thus compounds which can reduce the entry of calcium into these cells can be expected to assist in the prevention of such damage. Calcium build-up in cells can be caused by ischaemia (i.e. an inadequate supply of oxygen to the organ or part of the body containing the cells), and calcium-entry blockers, such as flunarizine and cinepazide, have been found to give a degree of protection against the deleterious effects of ischaemia, even when the drug is administered after the onset of ischaemia.

We have now discovered a series of new compounds structurally related to flunarizine, but which have significantly better pharmacological effects. In particular, they improve blood circulation, especially in the brain, are excellent selective calcium-entry and overload blockers and confer a significant degree of protection against morbidity arising from reduced oxygen intake, e.g. as a result of breathing an oxygen-poor atmosphere. Moreover, the compounds of the present invention have shown a significantly lower toxicity than do the prior art compounds.

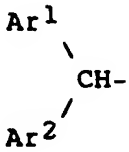
The compounds of the present invention are thus those compounds of formula (I):

A - M - B (I)

in which:

M represents a saturated heterocyclic group having from 5 to 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or being substituted at any of its carbon atoms by at least one C_1 - C_6 alkyl and/or oxo substituent;

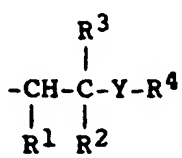
A represents a substituent on one of said nitrogen atoms and has the formula (II):



(II)

in which Ar^1 represents a phenyl group having a substituent X^1, and Ar^2 represents a phenyl group having a substituent X^2, where one of X^1 and X^2 represents a hydrogen atom or a halogen atom and the other of X^1 and X^2 represents a halogen atom;

B represents a substituent on the other nitrogen atom and has the formula (III):



(III)

in which: R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group;
R^2 and R^3 taken jointly represent an oxo group;
Y represents a group of formula $-NR^5-$;
R^4 and R^5 are the same or different and each represents a hydrogen atom, an aryl group, a C_1 – C_6 alkyl group, a substituted C_1 – C_6 alkyl group having at least one of substituents (a), a C_3 – C_{10} cycloalkyl group, an aromatic heterocyclic group or a C_2 – C_6 alkenyl group, or $-Y-R^4$ jointly represents a monocyclic heterocyclic group or a monocyclic heterocyclic group having an aromatic ring fused thereto;
said cycloalkyl groups are unsubstituted or have at least one C_1 – C_4 alkyl substituent, and are saturated or have at least one ethylenically unsaturated carbon – carbon double bond;
said aryl groups are carbocyclic aromatic groups having from 6 to 14 ring carbon atoms and are unsubstituted or have at least one of substituents (b) and/or substituents (c);
said aromatic heterocyclic groups have a heterocyclic ring containing from 5 to 7 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero – atoms or have said heterocyclic ring fused to a heterocyclic or carbocyclic ring having from 5 to 7 ring atoms, said aromatic heterocyclic groups being unsubstituted or having at least one of substituents (b) and/or substituents (d);
said monocyclic heterocyclic groups have from 4 to 12 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero – atoms and, where they are fused to an aromatic ring, said aromatic ring is a heterocyclic or carbocyclic ring having from 6 to 12 ring atoms, said monocyclic heterocyclic groups and said aromatic rings being unsubstituted or having at least one of substituents (b) and/or substituents (d);

substituents (a):

halogen atoms, aryl groups, hydroxy groups, C_1 – C_6 alkoxy groups, nitro groups, cyano groups, heterocyclic groups, carboxy groups, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups, aralkyloxycarbonyl groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups and heterocyclic carboxylic acyl groups;

substituents (b):

C_1 – C_4 alkyl groups, nitro groups, cyano groups, hydroxy groups, C_1 – C_4 alkoxy groups, aryloxy groups, aralkyloxy groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyloxy groups, C_1 – C_4 alkylthio groups, arylthio groups, aralkylthio groups where the alkyl part is C_1 – C_4, C_1 – C_4 alkylsulphinyl groups, C_1 – C_4 alkylsulphonyl groups, arylsulphinyl groups, arylsulphonyl groups, C_1 – C_7 aliphatic carboxylic acylamino groups, aromatic carboxylic acylamino groups, C_2 – C_7 alkoxycarbonylamino groups, aralkyloxycarbonylamino groups where the alkyl part is C_1 – C_4, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups, aralkyloxycarbonyl groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups, heterocyclic carboxylic acyl groups, carbamoyl groups, alkylcarbamoyl groups where the alkyl part is C_1 – C_4, dialkylcarbamoyl groups where each alkyl part is C_1 – C_4, thiocarbamoyl groups, alkyl(thiocarbamoyl) groups where the alkyl part is C_1 – C_4, dialkyl(thiocarbamoyl) groups where each alkyl part is C_1 – C_4, ureido groups, alkylureido groups where the alkyl part is C_1 – C_4, dialkylureido groups where each alkyl part is C_1 – C_4, thioureido groups, alkyl(thioureido) groups where the alkyl part is C_1 – C_4, dialkyl(thioureido) groups where each alkyl part is C_1 – C_4, C_3 – C_8 cycloalkyl groups, C_5 – C_8 cycloalkenyl groups, aryl groups, heterocyclic groups, halogen atoms, C_1 – C_6 alkyl groups having at least one halogen substituent, mercapto groups, amino groups, C_1 – C_4 alkylamino groups, dialkylamino groups where each alkyl part is C_1 – C_4, carboxy groups, (C_1 – C_4 hydroxyalkyl)amino groups, di(C_1 – C_4 hydroxyalkyl)amino groups, guanidino groups and guanidino groups having at least one C_1 – C_4 alkyl substituent;
PROVIDED THAT, where substituent (a) or (b) represents a group which itself is further substituted by a substituent selected from substituents (a) and (b), that further substituent is not yet further substituted;

substituents (c):

alkylenedioxy groups having from 1 to 6 carbon atoms;

substituents (d):

oxygen atoms;
and pharmaceutically acceptable salts thereof.

The compound wherein M represents an unsubstituted piperazine group, A is of the formula (II) wherein Ar^1 is 4-chlorophenyl and Ar^2 is phenyl, and B is of the formula (III) wherein R^1, R^4, and R^5 are hydrogen, and R^2, R^3 and Y are as defined, is excluded in that it is shown as Compound Number 18 in Table II at page 391 of an article J. Med. Chem. (1968). 11, 390-391.

The invention further provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

The invention still further provides the use for the manufacture of a medicament for the treatment of vascular disorders, especially cerebral vascular disorders, in an animal, especially a mammal, e.g. a human being, of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

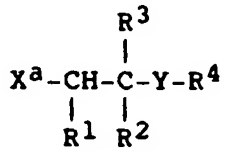
The invention still further provides the use for the manufacture of a medicament for the treatment of ischaemic disorders, especially cerebral ischaemic disorders, in an animal, especially a mammal, e.g. a human being, of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention still further provides the use for the manufacture of a medicament for protecting an animal, especially a mammal, e.g. a human being, against the deleterious effects of anoxia of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention still further provides a process for preparing a compound of the present invention, which process comprises reacting a compound of formula (IV):

A - M - H (IV)

(in which A and M are as defined above) or an active derivative thereof with a compound of formula (V):



(V)

(in which R^1, R^2, R^3 and R^4 are as defined above, and X^a represents a halogen atom, a carboxylic acyloxy group or a sulphonyloxy group), and optionally, where one or both of R^4 and R^5 represents a hydrogen atom, reacting the resulting compound with an appropriate reagent to introduce an alkyl, aryl, aralkyl, aromatic heterocyclic or alkenyl group on the nitrogen atom included in the definition of $-Y-R^4$.

In the compounds of the present invention, M represents a saturated heterocyclic group having from 5 to 7 ring atoms of which 2 are nitrogen atoms, the group being substituted or unsubstituted. Examples of suitable such heterocyclic groups include the imidazolidinyl, hexahydropyridazinyl, hexahydropyrimidinyl, piperazinyl, 1,2-diazacycloheptyl, 1,3-diazacycloheptyl and homopiperazinyl groups, of which the saturated heterocyclic groups containing 6 or 7 ring atoms are preferred, the piperazinyl and homopiperazinyl groups being more preferred.

Such heterocyclic groups may be substituted or unsubstituted, and, if substituted, the substituents are selected from oxygen atoms and C_1 - C_6 alkyl groups. which may be straight or branched chain groups. Examples of alkyl groups included amongst such substituents are the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, 2-methylbutyl, neopentyl, hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl and 2,3-dimethylbutyl groups, of which those alkyl groups containing from 1 to 4 carbon atoms are preferred.

There is no criticality as to the number of substituents on the heterocyclic group represented by M, and the only limit on the number of substituents is dictated by the number of substitutable positions and, in some cases, by steric constraints. We prefer those compounds having no more than 2 oxo substituents and/or no more than 4 alkyl substituents.

Where X^1 or X^2 represents a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom, of which the fluorine and chlorine atoms are preferred. One of X^1 and X^2 may be a halogen atom and the other may be a hydrogen atom, or both X^1 and X^2 may be halogen atoms. We especially prefer those compounds in which one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom or in which both X^1 and X^2 represent fluorine atoms. Preferably, where X^1 and/or X^2 represents a halogen atom, this is present on the phenyl group represented by Ar^1 and/or Ar^2 in the para position.

Where R^1 represents an alkyl group, this has from 1 to 6 carbon atoms, and may be a straight or branched chain group. Examples include those listed above as substituents on heterocyclic groups, the C_1

– C_4 alkyl groups being preferred, and the methyl group being most preferred.

Where R^4 or R^5 represents an aryl group, this may optionally be substituted with one or more of the substituents listed above as substituents (b) or (c), but preferably: lower (i.e. C_1 – C_6) alkyl groups; halogen atoms; lower alkoxy groups; or lower alkylenedioxy groups. As with the substituents on heterocyclic groups, there is, in principle, no restriction on the number of such substituents, except those dictated by the number of substitutable positions and steric constraints, but we generally find it convenient if, where the group is substituted, there are from 1 to 3 such substituents. Examples include such unsubstituted aryl groups as the phenyl or naphthyl (1– or 2– naphthyl) groups and corresponding groups which are substituted by one or more of the substituents listed above. For example, examples of groups having at least one alkyl substituent include the 4–methylphenyl, 2–methylphenyl, 3–methylphenyl, 4–ethylphenyl, 4–butylphenyl, 2–propylphenyl, 3–hexylphenyl, 2,3–dimethylphenyl, 3,4–dimethylphenyl, 2,5–dimethylphenyl, 2,6–dimethylphenyl, 2,4–dimethylphenyl, 2,3–diethylphenyl, 3,4–dipropylphenyl, 2,5–dibutylphenyl, 2,6–dipentylphenyl, 2,4–dihexylphenyl, 2,3,6–trimethylphenyl, 2,3,4–trimethylphenyl, 3,4,5–trimethylphenyl, 2,5,6–trimethylphenyl, 2,4,6–trimethylphenyl, 2,3,6–triethylphenyl, 2,3,4–tripropylphenyl, 3,4,5–tributylphenyl, 2,5,6–tripentylphenyl, 2,4,6–trihexylphenyl, 1–methyl–2–naphthyl, 2–methyl–1–naphthyl, 3–methyl–1–naphthyl, 2–ethyl–1–naphthyl, 1–butyl–2–naphthyl, 2–propyl–1–naphthyl, 3–hexyl–1–naphthyl, 2,3–dimethyl–1–naphthyl, 3,8–dimethyl–1–naphthyl, 4,8–dimethyl–1–naphthyl, 5,6–dimethyl–1–naphthyl, 2,4–dimethyl–1–cyclopentenyl, 2,3–diethyl–1–naphthyl, 3,4–dipropyl–1–naphthyl, 4,5–dibutyl–1–naphthyl, 5,6–dipentyl–1–naphthyl, 2,4–dihexyl–1–naphthyl, 2,3,6–trimethyl–1–naphthyl, 2,3,4–trimethyl–1–naphthyl, 3,4,5–trimethyl–1–naphthyl, 4,5,6–trimethyl–1–naphthyl, 2,4,8–trimethyl–1–naphthyl, 2,3,6–triethyl–1–naphthyl, 2,3,4–tripropyl–1–naphthyl, 3,4,8–tributyl–1–naphthyl, 4,5,6–tripentyl–1–naphthyl and 2,4,6–trihexyl–1–naphthyl groups. Examples of aryl groups having at least one halogen substituent include the 4–fluorophenyl, 2–fluorophenyl, 3–fluorophenyl, 4–chlorophenyl, 4–bromophenyl, 2–iodophenyl, 3–chlorophenyl, 3,5–difluorophenyl, 2,5–difluorophenyl, 2,5–diiodophenyl, 2,6–difluorophenyl, 2,4–difluorophenyl, 2,3–dichlorophenyl, 3,4–dichlorophenyl, 2,5–dichlorophenyl, 2,6–dichlorophenyl, 2,4–dibromophenyl, 2,3,6–trifluorophenyl, 2,3,4–trifluorophenyl, 3,4,5–trifluorophenyl, 2,5,6–trifluorophenyl, 2,4,6–trifluorophenyl, 2,3,6–trichlorophenyl, 2,3,4–trichlorophenyl, 3,4,5–tribromophenyl, 2,5,6–tribromophenyl, 2,4,6–tribromophenyl, 1–fluoro–2–naphthyl, 2–fluoro–1–naphthyl, 3–fluoro–1–naphthyl, 2–chloro–1–naphthyl, 1–chloro–2–naphthyl, 2–bromo–1–naphthyl, 3–bromo–1–naphthyl, 2,3–difluoro–1–naphthyl, 3,8–difluoro–1–naphthyl, 4,8–difluoro–1–naphthyl, 5,6–difluoro–1–naphthyl, 2,4–difluoro–1–naphthyl, 2,3–dichloro–1–naphthyl, 3,4–dichloro–1–naphthyl, 4,5–dichloro–1–naphthyl, 5,6–dibromo–1–naphthyl, 2,4–dibromo–1–naphthyl, 2,3,6–trifluoro–1–naphthyl, 2,3,4–trifluoro–1–naphthyl, 3,4,5–trifluoro–1–naphthyl, 4,5,6–trifluoro–1–naphthyl, 2,4,8–trifluoro–1–naphthyl, 2,3,6–trichloro–1–naphthyl, 2,3,4–trichloro–1–naphthyl, 3,4,8–tribromo–1–naphthyl, 4,5,6–tribromo–1–naphthyl and 2,4,6–tribromo–1–naphthyl groups. Examples of aryl groups having at least one lower alkoxy substituent include the 4–methoxyphenyl, 2–methoxyphenyl, 3–methoxyphenyl, 4–ethoxyphenyl, 4–propoxyphenyl, 2–butoxyphenyl, 3–ethoxyphenyl, 3,5–dimethoxyphenyl, 2,5–dimethoxyphenyl, 2,5–dipropoxyphenyl, 2,6–dimethoxyphenyl, 2,4–dimethoxyphenyl, 2,3–diethoxyphenyl, 3,4–diethoxyphenyl, 2,5–diethoxyphenyl, 2,6–diethoxyphenyl, 2,4–dipropoxyphenyl, 2,3,6–trimethoxyphenyl, 2,3,4–trimethoxyphenyl, 3,4,5–trimethoxyphenyl, 2,5,6–methoxyphenyl, 2,4,6–trimethoxyphenyl, 2,3,6–triethoxyphenyl, 2,3,4–triethoxyphenyl, 3,4,5–tripropoxyphenyl, 2,5,6–tripropoxyphenyl, 2,4,6–tripropoxyphenyl, 1–methoxy–2–naphthyl, 2–methoxy–1–naphthyl, 3–methoxy–1–naphthyl, 2–ethoxy–1–naphthyl, 1–ethoxy–2–naphthyl, 2–propoxy–1–naphthyl, 3–propoxy–1–naphthyl, 2,3–dimethoxy–1–naphthyl, 3,8–dimethoxy–1–naphthyl, 4,8–dimethoxy–1–naphthyl, 5,6–dimethoxy–1–naphthyl, 2,4–dimethoxy–1–naphthyl, 2,3–diethoxy–1–naphthyl, 3,4–diethoxy–1–naphthyl, 4,5–diethoxy–1–naphthyl, 5,6–dipropoxy–1–naphthyl, 2,4–dipropoxy–1–naphthyl, 2,3,6–trimethoxy–1–naphthyl, 2,3,4–trimethoxy–1–naphthyl, 3,4,5–trimethoxy–1–naphthyl, 4,5,6–trimethoxy–1–naphthyl, 2,4,8–trimethoxy–1–naphthyl, 2,3,6–triethoxy–1–naphthyl, 2,3,4–triethoxy–1–naphthyl, 3,4,8–tripropoxy–1–naphthyl, 4,5,6–tripropoxy–1–naphthyl and 2,4,6–tripropoxy–1–naphthyl groups. Examples of aryl groups having at least one (and preferably only one) lower alkylenedioxy substituent include the 2,3–methylenedioxyphenyl, 3,4–methylenedioxyphenyl, 2,3–ethylenedioxyphenyl, 3,4–ethylenedioxyphenyl, 2,3–methylenedioxy–1–naphthyl, 3,4–methylenedioxy–1–naphthyl, 5,6–methylenedioxy–1–naphthyl, 6,7–methylenedioxy–1–naphthyl, 7,8–methylenedioxy–1–naphthyl, 3,4–methylenedioxy–2–naphthyl, 5,6–methylenedioxy–2–naphthyl, 6,7–methylenedioxy–2–naphthyl and 7,8–methylenedioxy–2–naphthyl groups. Where the aryl group has two or more substituents, these may, if desired, be selected from two or more different classes of the substituents described above. However, we most prefer either unsubstituted aryl groups or phenyl groups having at least one, and

preferably from 1 to 3, substituents selected from lower alkyl groups, halogen atoms, lower alkoxy groups and lower alkylenedioxy groups.

Where R^4 or R^5 represents an alkyl group, this has from 1 to 6 carbon atoms, and may be a straight or branched chain group. Examples include those listed above as substituents on heterocyclic groups, the C_1 – C_4 alkyl groups being preferred, and the C_1 – C_3 alkyl groups being most preferred. Such alkyl groups may be substituted or unsubstituted, and, if substituted, the substituents are selected from substituents (a), defined above and exemplified in greater detail below. Depending on the nature of the substituent, there is normally no criticality as to the number of substituents, and, as explained in relation to other substituted groups, the only constraint will normally arise from the number of substitutable positions and possibly steric constraints. In general, provided that there are sufficient substitutable positions, the number of substituents will preferably be from 1 to 5, more preferably from 1 to 3. Where the substituent is an aryl group, the number is preferably 1 or 2, and the resulting aralkyl groups are preferably as discussed below.

Where R^4 or R^5 represents such an aralkyl group, this may optionally be substituted on the aryl ring with one or more of the substituents listed above as substituents (b) or (c), but preferably: lower alkyl groups; halogen atoms; lower alkoxy groups; or lower alkylenedioxy groups. As with the substituents on aryl groups, there is, in principle, no restriction on the number of such substituents, except those dictated by the number of substitutable positions and steric constraints, but we generally find it convenient if, where the group is substituted, there are from 1 to 3 such substituents. The alkyl part is preferably a C_1 – C_4 alkyl group, more preferably a methyl, ethyl or propyl group, which is preferably otherwise unsubstituted. Examples of such aralkyl groups include such unsubstituted aralkyl groups as the benzyl, phenethyl, 1-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 4-phenylbutyl and benzhydryl groups and such substituted aralkyl groups as the chlorobenzyl, methylbenzyl and dimethylbenzyl groups.

Where R^4 or R^5 represents a C_3 – C_{10} cycloalkyl group, this may be a monocyclic or polycyclic (e.g. bicyclic or tricyclic) group which may be unsubstituted or may be substituted by at least one C_1 – C_4 alkyl group and may be saturated or have at least one ethylenic carbon-carbon double bond. Included amongst such groups are the simple cycloalkyl groups as well as cyclic terpenyl groups, and, especially in the case of the terpenyl groups, the free valence by which the group is attached to the rest of the molecule may be present on a ring carbon atom or on one of the side chain carbon atoms. Examples of such groups include the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 8,9,10-trinorbornyl (still commonly known as "norbornyl"), 3-pinanyl (sometimes known as "isopinocamphenyl"), 2(3)-pinen-2-yl (sometimes known as "myrtamyl") and adamantyl groups, of which those cycloalkyl groups containing from 6 to 10 carbon atoms are preferred.

Where R^4 or R^5 represents an aromatic heterocyclic group, this has from 5 to 7 ring atoms, and may be substituted or unsubstituted. If substituted, the substituents are selected from substituents (b) and (d), as defined above and exemplified in greater detail below. The group may be monocyclic or fused polycyclic (e.g. bicyclic), and, if it is polycyclic, at least one of the rings (and optionally more than one of the rings) contains at least one nitrogen and/or oxygen and/or sulphur hetero-atom. Examples of such heterocyclic groups include the furyl, thienyl, pyrrolyl, azepinyl, morpholinyl, thiomorpholinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, acridyl and tetrahydroacridyl groups. More preferred groups are heterocyclic groups containing from 5 to 7 ring atoms of which at least one is a nitrogen atom, optionally together with at least one oxygen and/or sulphur atom; examples include the pyrrolyl, azepinyl, morpholinyl, thiomorpholinyl, pyrazolyl, imidzaolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, acridyl and tetrahydroacridyl groups, the most preferred groups being the imidazolyl, oxazolyl, isoxazolyl, thiazolyl, quinolyl, isoquinolyl, acridyl and tetrahydroacridyl groups.

Where R^4 or R^5 represents an alkenyl group, this has from 2 to 6 carbon atoms and may be a straight or branched chain group. Examples of such groups include the vinyl, allyl, 1-propenyl, 1-butenyl, 2-butenyl and 3-butenyl groups, of which those alkenyl groups containing from 2 to 4 carbon atoms are preferred.

Where $-Y-R^4$ represents a monocyclic heterocyclic group or a monocyclic heterocyclic group having an aromatic ring fused thereto, the heterocyclic group contains from 4 to 12 hetero-atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, and this ring may be monocyclic or polycyclic. The group may be substituted or unsubstituted. If substituted, the substituents are selected from substituents (b) and (d), as defined above and exemplified in greater detail below. If the group is fused with an aromatic ring, the aromatic ring is a heterocyclic or carbocyclic ring having from 6 to 12 ring atoms. Examples of such groups include the 1-pyrrolidinyl, piperidino, 1-tetrahydroquinolyl, tetrahydroisoquinolyl, isoindolyl, indolinyl and 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl groups.

Where substituent (a) or (b) is a halogen atom, this is preferably a fluorine, chlorine, bromine or iodine atom.

Where substituent (a) is an alkoxycarbonyl group, the alkyl part thereof is a C_1 – C_6 alkyl group, e.g. as exemplified above in relation to substituents on heterocyclic groups. Specific examples of such alkoxycarbonyl groups include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl and t-butoxycarbonyl groups. The preferred such group is the ethoxycarbonyl group.

Where substituent (a) is an alkoxy group, this may be a straight or branched chain group containing from 1 to 6 carbon atoms, and examples include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, isopentyloxy, 2-methylbutoxy, neopentyloxy, hexyloxy, 4-methylpentyloxy, 3-methylpentyloxy, 2-methylpentyloxy, 3,3-dimethylbutoxy, 2,2-dimethylbutoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy and 2,3-dimethylbutoxy groups.

Where substituent (a) is a heterocyclic group, this may be any one of the aromatic heterocyclic groups, monocyclic heterocyclic groups and monocyclic heterocyclic groups having an aromatic ring fused thereto exemplified in relation to R^4 and R^5.

Where substituent (a) is an aryloxycarbonyl group or an aralkyloxycarbonyl group where the alkyl part is C_1 – C_4, the aryl or aralkyl part is preferably as defined and exemplified above in relation to the aryl and aralkyl groups which may be represented by R^4 and R^5.

Where substituent (a) is an aliphatic carboxylic acyl group, this may be a straight or branched chain group, and examples include the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, acryloyl, propioloyl, methacryloyl and crotonoyl groups.

Where substituent (a) is an aromatic carboxylic acyl group, this is an arylcarbonyl group in which the aryl part may be as defined and exemplified above in relation to the aryl groups which may be represented by R^4 and R^5. Examples include the benzoyl and naphthoyl groups and substituted analogues thereof.

Where substituent (a) is a heterocyclic carboxylic acyl group, this is a heterocyclic-carbonyl group in which the heterocyclic part may be as defined and exemplified above in relation to the heterocyclic groups which may be represented by R^4 and R^5. Examples include the nicotinoyl and isonicotinoyl groups.

Examples of groups which may be represented by substituent (b) include:

such C_1 – C_4 alkyl groups as the methyl, ethyl, propyl, isopropyl and butyl groups;

the nitro, cyano, hydroxy, mercapto, carbamoyl, thiocarbamoyl, ureido, guanidino, amino and carboxy groups;

C_1 – C_4 alkoxy groups, such as those exemplified above in relation to substituents (a);

aryloxy groups and aralkyloxy groups where the alkyl part is C_1 – C_4, such as those corresponding to the aryl and aralkyl groups exemplified above;

C_1 – C_7 aliphatic carboxylic acyloxy groups, C_1 – C_7 aliphatic carboxylic acylamino groups, aromatic carboxylic acyloxy groups and aromatic carboxylic acylamino groups, such as those corresponding to the acyl groups exemplified above;

C_1 – C_4 alkylthio groups, arylthio groups, aralkylthio groups where the alkyl part is C_1 – C_4, C_1 – C_4 alkylsulphinyl groups, C_1 – C_4 alkylsulphonyl groups, arylsulphinyl groups and arylsulphonyl groups, such as those corresponding to the alkyl and aryl groups exemplified above;

C_2 – C_7 alkoxycarbonylamino groups, aralkyloxycarbonylamino groups, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups and aralkyloxycarbonyl groups, such as those corresponding to the alkoxy, aralkyl and aryl groups exemplified above;

C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups and heterocyclic carboxylic acyl groups, such as those exemplified above;

alkylcarbamoyl, dialkylcarbamoyl, alkyl(thiocarbamoyl), dialkyl(thiocarbamoyl), alkylureido, dialkylureido, thioureido groups, alkylamino, dialkylamino, hydroxyalkylamino, dihydroxyalkylamino, alkylguanidino, alkyl-(thioureido) and dialkyl(thioureido) groups where the alkyl part(s) are as exemplified above;

C_3 – C_8 cycloalkyl groups, such as the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups;

C_5 – C_8 cycloalkenyl groups, such as the cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl groups;

aryl groups and heterocyclic groups, such as those exemplified above; and

C_1 – C_6 alkyl groups having at least one halogen substituent, such as the chloromethyl, fluoromethyl, trifluoromethyl, 2-iodoethyl, 2,2,2-trichloroethyl and 2,2,2-trifluoroethyl groups.

The compounds of the present invention contain asymmetric carbon atoms in their molecules, and can, therefore, exist in the form of various stereoisomers, in which each of these asymmetric carbon atoms can be in the R-, or S-, configuration. The individual isomers may be prepared by stereo-specific synthesis

techniques, such as are well known in the art, or a mixture of isomers may be prepared and then, if desired, separated by well known resolution techniques. Alternatively, the compounds may be employed as mixtures of two or more such isomers. It is well known that pharmacologically active compounds often exhibit greater activity in the form of specific isomers, and, if desired, simple experimentation will reveal which, if any, of the isomers of the compounds of the present invention is the more active.

The compounds of the present invention contain in their molecules certain basic nitrogen atoms and can, therefore, form salts with acids. There is no limitation upon the nature of such salts, provided that, where they are to be used for therapeutic purposes, they are pharmaceutically acceptable, which, as is well-known in the art, means that they do not have reduced activity (or unacceptably reduced activity) or increased toxicity (or unacceptably increased toxicity) compared with the free compound of formula (I). Where, however, they are to be used for non-therapeutic purposes, e.g. as intermediates in the preparation of other compounds, even this limitation does not apply. Examples of suitable acids include: inorganic acids, such as hydrohalic acids (e.g. hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid), nitric acid, perchloric acid, sulphuric acid and phosphoric acid; organic sulphonic acids, such as the lower alkylsulphonic acids (e.g. methanesulphonic acid, trifluoromethanesulphonic acid or ethanesulphonic acid) and arylsulphonic acids (e.g. benzenesulphonic acid or p-toluenesulphonic acid); organic carboxylic acids, such as fumaric acid, succinic acid, citric acid, tartaric acid, oxalic acid and maleic acid; and amino acids, such as glutamic acid or aspargic acid.

Preferred classes of compounds of the present invention are those compounds of formula (I) and pharmaceutically acceptable salts thereof, in which:

(A) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 - C_6 alkyl and/or oxo substituents.

(B) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 - C_4 alkyl and/or oxo substituents.

(C) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 - C_4 alkyl and/or oxo substituents.

(D) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 - C_4 alkyl and/or oxo substituents.

(E) At least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position.

(F) R^1 represents a hydrogen atom or a C_1 - C_4 alkyl group.

(G) R^1 represents a hydrogen atom or a C_1 - C_2 alkyl group.

(H) R^1 represents a hydrogen atom or a methyl group.

(I) One of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and the other represents a C_6 - C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 - C_{10}, a C_6 - C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

(J) One of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 - C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b) and/or (c).

(K) Both of X^1 and X^2 represent fluorine atoms.

(L) One of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom.

(M) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 - C_6 alkyl and/or oxo substituents; and

at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;

R^1 represents a hydrogen atom or a C_1 - C_6 alkyl group; and

one of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and the other represents a C_6 - C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 - C_{10}, a C_6 - C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

(N) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 - C_4 alkyl and/or oxo substituents;

at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;

R^1 represents a hydrogen atom or a C_1 - C_4 alkyl group; and

one of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and

the other represents a C_6 – C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 – C_{10}, a C_6 – C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

(O) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one substituent selected from substituents (b) and (c).

(P) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 substituents selected from C_3 – C_4 alkyl groups and oxo groups;
both of X^1 and X^2 represent fluorine atoms;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one substituent selected from substituents (b).

(Q) M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one substituent selected from substituents (b).

(R) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

(S) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

(T) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

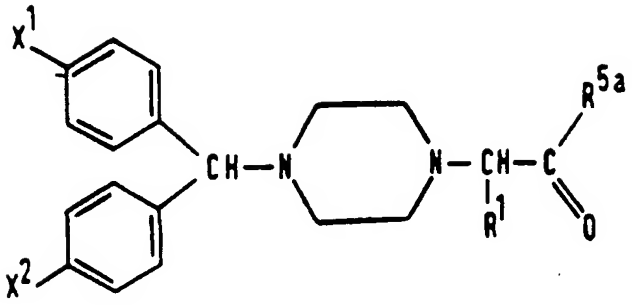
(U) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
both of X^1 and X^2 represent fluorine atoms;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

(V) M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom;

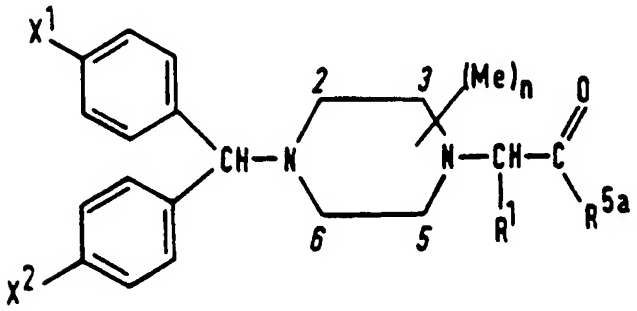
R^1 represents a hydrogen atom or a C_1 - C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 - C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

Examples of specific compounds of the invention are given in the following formulae (I-1) to (I-4)and (I-6) to (I-9), in which the substituents are as defined in the corresponding one of Tables 1 to 4 and 6 to 9 [i.e. Table 1 relates to formula (I-1), Table 2 relates to formula (I-2) and so on]. There are no Tables 5 or 10. In the Tables, the following abbreviations are used:

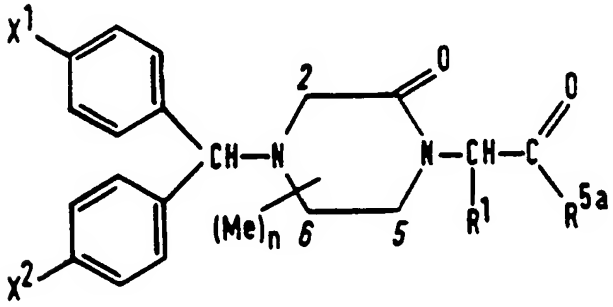
AD	adamantyl. i.e. 1AD is 1-adamantyl and 2AD is 2-adamantyl
All	allyl
Bu	butyl
iBu	isobutyl
Bz	benzyl
DB	1,1-dimethylbenzyl
DFP	difluorophenyl, i.e. 2,5DFP is 2,5-difluorophenyl, 3,5DFP is 3,5-difluorophenyl and 2,6DFP is 2,6-difluorophenyl
DMP	3,5-dimethoxyphenyl
ECM	ethoxycarbonylmethyl
Et	ethyl
FP	fluorophenyl, i.e. 2FP is 2-fluorophenyl, 3FP is 3-fluorophenyl and 4FP is 4-fluorophenyl
Fur	furyl
Hx	hexyl
cHx	cyclohexyl
ID	2-isoindolyl
4MB	4-methoxybenzyl
MDP	3,4-methylenedioxyphenyl
Me	methyl
4MP	4-methoxyphenyl
Np	naphthyl
Pn	pentyl
cPn	cyclopentyl
4PP	4-propoxyphenyl
Pr	propyl
Pym	pyrimidyl
Pyr	pyridyl
Pyrd	pyrrolidinyl
TAO	N-(1,3,3-trimethyl-6-azabicyclo-[3.2.1]octyl)
Thiz	thiazolyl
THQ	tetrahydroquinolyl
TM	2,4,6-trimethylphenyl
TMP	3,4,5-trimethoxyphenyl
TP	2,4,5-trimethoxyphenyl



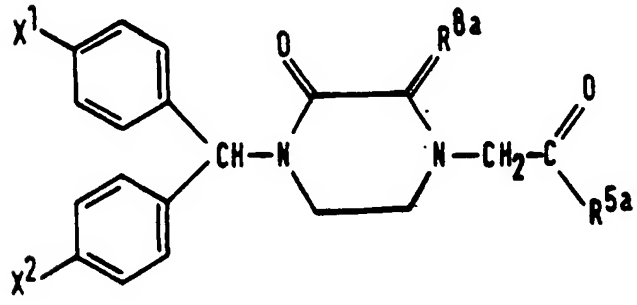
(I-1)



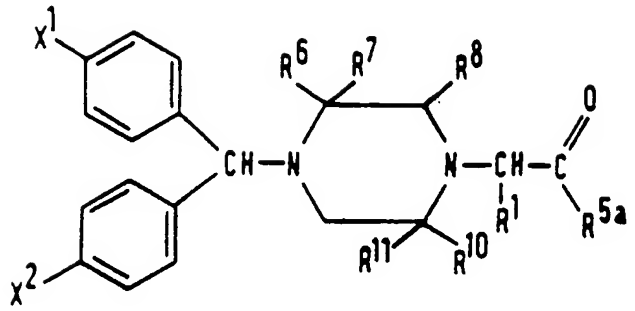
(I-2)



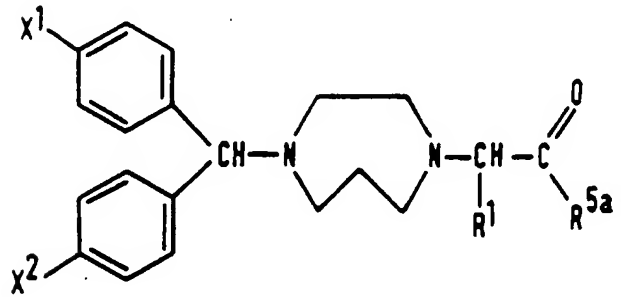
(I-3)



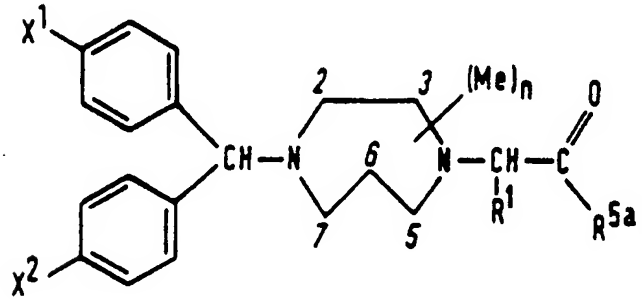
(I-4)



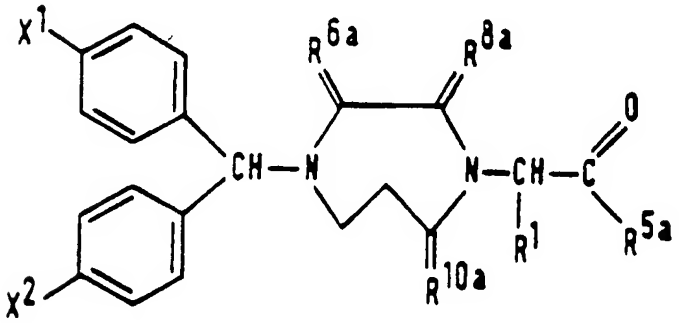
(I-6)



(I-7)



(I-8)



(I-9)

TABLE 1

Cpd No.	X^1	X^2	R^1	R^{5a}
1-1	F	F	H	1-Pyrd
1-2	F	F	H	THQ
1-3	F	F	H	TAO
1-4	F	F	H	DMP-NH
1-5	F	F	H	4MP-NH
1-6	F	F	H	iBu-NH
1-7	F	F	H	TMP-NH
1-8	F	F	H	Bz-NH
1-9	F	F	H	1-Np-NH
1-10	F	F	H	cHx-NH
1-11	F	F	H	TM-NH
1-12	F	F	H	DB-NH
1-13	F	F	H	3FP-NH
1-14	F	F	H	2FP-NH
1-15	F	F	H	4PP-NH
1-16	F	F	H	ECM-NH
1-17	F	F	H	1AD-NH
1-18	F	F	H	MDP-NH
1-19	F	F	H	2AD-NH
1-20	F	F	H	4FP-NH
1-21	F	F	H	3,5DFP-NH
1-22	F	F	H	2-Pym-NH
1-23	F	F	H	Et-NH
1-24	F	F	H	2-Fur-NH
1-25	F	F	H	2-Thiz-NH
1-26	F	F	H	2,6DFP-NH
1-27	F	F	H	3FP-N-All
1-28	F	F	H	3FP-N-Me
1-29	F	F	H	ID

TABLE 1 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
1-30	F	F	H	4MB-NH
1-31	F	F	H	TP-NH
1-32	F	F	H	2,5DFP-NH
1-33	F	F	H	2-Pyr-NH
1-34	F	F	H	cPn-NH
1-35	F	F	H	2,4DFP-NH
1-36	F	F	Me	ID
1-37	F	F	Me	THQ
1-38	F	F	Et	TAO
1-39	F	F	Me	DMP-NH
1-40	F	F	Bu	4MP-NH
1-41	F	F	Me	1-Np-NH
1-42	F	F	Me	TM-NH
1-43	F	F	Et	DB-NH
1-44	F	F	Me	3FP-NH
1-45	F	F	Bu	2FP-NH
1-46	F	F	Pn	4PP-NH
1-47	F	F	Hx	ECM-NH
1-48	F	F	Me	1AD-NH
1-49	F	F	Me	3,5DFP-NH
1-50	F	F	Me	2-Pym-NH
1-51	F	F	Me	Et-NH
1-52	F	F	Me	2-Fur-NH
1-53	F	F	Me	2-Thiz-NH
1-54	F	F	Me	2,6DFP-NH
1-55	F	F	Me	3FP-N-All
1-56	F	F	Me	3FP-N-Me
1-57	F	F	Me	ID
1-58	F	F	Me	4MB-NH

TABLE 1 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
1-59	F	F	Me	1-Np-NH
1-60	F	F	Me	TP-NH
1-61	F	F	Me	2,5DFP-NHO
1-62	F	F	Me	2-Pyr-NH
1-63	F	F	Me	cPn-NH
1-64	F	F	Me	2,4DFP-NH
1-65	Cℓ	H	H	1-Pyrd
1-66	Cℓ	H	H	THQ
1-67	Cℓ	H	H	TAO
1-68	Cℓ	H	H	DMP-NH
1-69	Cℓ	H	H	4MP-NH
1-70	Cℓ	H	H	iBu-NH
1-71	Cℓ	H	H	TMP-NH
1-72	Cℓ	H	H	Bz-NH
1-73	Cℓ	H	H	1-Np-NH
1-74	Cℓ	H	H	cHx-NH
1-75	Cℓ	H	H	TM-NH
1-76	Cℓ	H	H	DB-NH
1-77	Cℓ	H	H	3FP-NH
1-78	Cℓ	H	H	2FP-NH
1-79	Cℓ	H	H	4PP-NH
1-80	Cℓ	H	H	ECM-NH
1-81	Cℓ	H	H	1AD-NH
1-82	Cℓ	H	H	MDP-NH
1-83	Cℓ	H	H	2AD-NH
1-84	Cℓ	H	H	4FP-NH
1-85	Cℓ	H	H	3,5DFP-NH
1-86	Cℓ	H	H	2-Pym-NH
1-87	Cℓ	H	H	Et-NH

TABLE 1 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
1-88	Cℓ	H	H	2-Fur-NH
1-89	Cℓ	H	H	2-Thiz-NH
1-90	Cℓ	H	H	2,6DFP-NH
1-91	Cℓ	H	H	3FP-N-All
1-92	Cℓ	H	H	3FP-N-Me
1-93	Cℓ	H	H	ID
1-94	Cℓ	H	H	4MB-NH
1-95	Cℓ	H	H	1-Np-NH
1-96	Cℓ	H	H	TP-NH
1-97	Cℓ	H	H	2,5DFP-NH
1-98	Cℓ	H	H	2-Pyr-NH
1-99	Cℓ	H	H	cPn-NH
1-100	Cℓ	H	H	2,4DFP-NH
1-101	Cℓ	H	Me	1-Pyrd
1-102	Cℓ	H	Me	THQ
1-103	Cℓ	H	Et	TAO
1-104	Cℓ	H	Pr	DMP-NH
1-105	Cℓ	H	Bu	4MP-NH
1-106	Cℓ	H	Pn	iBu-NH
1-107	Cℓ	H	Hx	TMP-NH
1-108	Cℓ	H	Et	DB-NH
1-109	Cℓ	H	Pr	3PP-NH
1-110	Cℓ	H	Bu	2PP-NH
1-111	Cℓ	H	Pn	4PP-NH
1-112	Cℓ	H	Hx	ECM-NH
1-113	Cℓ	H	Me	3,5DFP-NH
1-114	Cℓ	H	Me	2-Pym-NH
1-115	Cℓ	H	Me	Et-NH
1-116	Cℓ	H	Me	2-Fur-NH

TABLE 1 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
1-117	Cℓ	H	Me	2-Thiz-NH
1-118	Cℓ	H	Me	2,6DFP-NH
1-119	Cℓ	H	Me	3FP-N-All
1-120	Cℓ	H	Me	3FP-N-Me
1-121	Cℓ	H	Me	ID
1-122	Cℓ	H	Me	4MB-NH
1-123	Cℓ	H	Me	1-Np-NH
1-124	Cℓ	H	Me	2,5DFP-NH
1-125	Cℓ	H	Me	2-Pyr-NH
1-126	Cℓ	H	Me	cPn-NH
1-127	Cℓ	H	Me	2,4DFP-NH

TABLE 2

Cpd No.	X^1	X^2	R^1	R^{5a}	n	position of $(Me)_n$
2-1	F	F	Me	2FP-NH	2	2,5
2-2	F	F	Me	TM-NH	2	2,5
2-3	F	F	H	3FP-NH	1	2
2-4	F	F	H	1-Pyrd	1	2
2-5	F	F	H	1AD-NH	2	2,5
2-6	F	F	H	TAO	1	3
2-7	F	F	H	4MP-NH	2	2,5
2-8	F	F	H	TM-NH	2	2,5
2-9	F	F	H	TMP-NH	2	2,5
2-10	F	F	H	2,5DFP-NH	2	2,5
2-11	F	F	H	TM-NH	1	3
2-12	F	F	H	3FP-NH	1	3
2-13	F	F	H	TMP-NH	1	3
2-14	F	F	H	2FP-NH	1	3
2-15	F	F	H	4FP-NH	1	3
2-16	F	F	H	2FP-NH	2	2,5
2-17	F	F	H	1-Np-NH	2	2,5
2-18	F	F	H	cHx-NH	3	2,2,3
2-19	F	F	H	3FP-NH	2	3,3
2-20	F	F	H	DB-NH	4	2,3,5,6
2-21	F	F	H	3FP-NH	2	2,5
2-22	F	F	H	4FP-NH	2	2,5
2-23	F	F	H	4PP-NH	2	2,5
2-24	F	F	H	ECM-NH	2	2,5
2-25	Cℓ	H	H	1-Pyrd	1	2
2-26	Cℓ	H	H	THQ	2	2,2
2-27	Cℓ	H	H	TAO	3	2,2,5
2-28	Cℓ	H	H	DMP-NH	4	2,2,5,5
2-29	Cℓ	H	H	4MP-NH	2	2,5

TABLE 2 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}	n	position of $(Me)_n$
2-30	Cℓ	H	H	iBu-NH	3	2,5,5
2-31	Cℓ	H	H	TMP-NH	2	5,5
2-32	Cℓ	H	H	Bz-NH	2	2,3
2-33	Cℓ	H	H	1-Np-NH	1	3
2-34	Cℓ	H	H	cHx-NH	3	2,2,3
2-35	Cℓ	H	H	TM-NH	4	2,2,3,3
2-36	Cℓ	H	H	DB-NH	4	2,3,5,6
2-37	F	Cℓ	H	1-Pyrd	1	2
2-38	F	Cℓ	H	THQ	2	2,2
2-39	F	Br	H	TAO	3	2,2,5
2-40	F	Cℓ	H	DMP-NH	4	2,2,5,5
2-41	F	H	H	4MP-NH	2	2,5
2-42	F	H	H	iBu-NH	3	2,5,5
2-43	F	Cℓ	H	TMP-NH	2	5,5
2-44	F	Br	H	Bz-NH	2	2,3
2-45	F	H	H	1-Np-NH	1	3
2-46	F	Cℓ	H	cHx-NH	3	2,2,3
2-47	F	Br	H	TM-NH	4	2,2,3,3
2-48	F	H	H	DB-NH	4	2,3,5,6
2-49	Cℓ	Cℓ	H	1-Pyrd	1	2
2-50	Cℓ	Cℓ	H	THQ	2	2,2
2-51	Cℓ	Br	H	TAO	3	2,2,5
2-52	Cℓ	Cℓ	H	DMP-NH	4	2,2,5,5
2-53	Cℓ	Cℓ	H	4MP-NH	2	2,5
2-54	Cℓ	Br	H	iBu-NH	3	2,5,5
2-55	Cℓ	Cℓ	H	TMP-NH	2	5,5
2-56	Cℓ	Cℓ	H	Bz-NH	2	2,3
2-57	Cℓ	Br	H	1-Np-NH	1	3
2-58	Cℓ	Cℓ	H	cHx-NH	3	2,2,3

TABLE 2 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}	n	position of $(Me)_n$
2-59	Cℓ	Cℓ	H	TM-NH	4	2,2,3,3
2-60	Cℓ	Cℓ	H	DB-NH	4	2,3,5,6
2-61	F	F	Et	3FP-NH-All	3	2,2,3
2-62	F	F	Me	TM-NH	1	3
2-63	F	F	Me	2,6DFP-NH	1	3
2-64	F	F	Me	1-Np-NH	1	3
2-65	F	F	Me	3FP-NH-Me	4	2,2,3,3
2-66	F	H	Me	2,5DFP-NH	3	2,3,3
2-67	Cℓ	Cℓ	Et	2-Pyr-NH	3	2,3,5

TABLE 3

Cpd No.	X^1	X^2	R^1	R^{5a}	n	position of $(Me)_n$
3-1	F	F	H	1AD-NH	1	2
3-2	F	F	H	TM-NH	0	-
3-3	Cℓ	H	H	2FP-NH	0	-
3-4	Cℓ	H	H	ECM-NH	1	2
3-5	Cℓ	H	H	1AD-NH	2	2,5
3-6	F	H	H	2FP-NH	0	-
3-7	F	H	H	ECM-NH	1	2
3-8	F	Cℓ	H	1AD-NH	2	2,5
3-9	F	F	Me	TM-NH	0	-
3-10	F	F	Me	1AD-NH	0	-
3-11	F	F	Me	3FP-NH	0	-

TABLE 4

Cpd No.	X^1	X^2	R^{5a}	R^{8a}
4-1	Cℓ	H	3FP-NH	H_2
4-2	Cℓ	H	4PP-NH	O
4-3	F	Cℓ	3FP-NH	H_2
4-4	F	H	4PP-NH	O

TABLE 6

Cpd No.	X^1	X^2	R^1	R^{5a}	R^6	R^7	R^8	R^{10}	R^{11}
6-1	F	F	Et	ID	Et	H	H	Me	H
6-2	Cℓ	H	Et	4MB-NH	H	H	H	Me	H
6-3	Cℓ	H	Me	1-Np-NH	H	H	H	Pr	Me
6-4	Cℓ	H	Me	TP-NH	Me	Me	H	Et	Me
6-5	F	H	Et	cPn-NH	Et	H	H	H	H
6-6	Cℓ	H	Me	2,4DFP-NH	Et	H	Et	H	H

TABLE 7

Cpd No.	X^1	X^2	R^1	R^{5a}
7-1	F	F	H	1-Pyrd
7-2	F	F	H	THQ
7-3	F	F	H	TAO
7-4	F	F	H	DMP-NH
7-5	F	F	H	4MP-NH
7-6	F	F	H	iBu-NH
7-7	F	F	H	TMP-NH
7-8	F	F	H	Bz-NH
7-9	F	F	H	1-Np-NH
7-10	F	F	H	cHx-NH5
7-11	F	F	H	TM-NH
7-12	F	F	H	DB-NH
7-13	F	F	H	3FP-NH
7-14	F	F	H	2FP-NH
7-15	F	F	H	4PP-NH
7-16	F	F	H	ECM-NH
7-17	F	F	H	1AD-NH
7-18	F	F	H	MDP-NH
7-19	F	F	H	2AD-NH
7-20	F	F	H	4FP-NH
7-21	F	F	H	3,5DFP-NH
7-22	F	F	H	2-Pym-NH
7-23	F	F	H	Et-NH
7-24	F	F	H	2-Fur-NH
7-25	F	F	H	2-Thiz-NH
7-26	F	F	H	2,6DFP-NH
7-27	F	F	H	3FP-N-All
7-28	F	F	H	3FP-N-Me
7-29	F	F	H	ID

TABLE 7 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
7-30	F	F	H	4MB-NH
7-31	F	F	H	1-Np-NH
7-32	F	F	H	TP-NH
7-33	F	F	H	2,5DFP-NH
7-34	F	F	H	2-Pyr-NH
7-35	F	F	H	cPn-NH
7-36	F	F	H	2,4DFP-NH
7-37	F	F	Me	1-Pyrd
7-38	F	F	Me	THQ
7-39	F	F	Et	TAO
7-40	F	F	Me	DMP-NH
7-41	F	F	Bu	4MP-NH
7-42	F	F	Pn	iBu-NH
7-43	F	F	Hx	TMP-NH
7-44	F	F	Me	1-Np-NH
7-45	F	F	Me	TM-NH
7-46	F	F	Et	DB-NH
7-47	F	F	Pr	3FP-NH
7-48	F	F	Bu	4FP-NH
7-49	F	F	Bu	2FP-NH
7-50	F	F	Pn	4PP-NH
7-51	F	F	Hx	ECM-NH
7-52	F	F	Me	1AD-NH
7-53	F	F	Me	3,5DFP-NH
7-54	F	F	Me	2-Pym-NH
7-55	F	F	Me	Et-NH
7-56	F	F	Me	2-Fur-NH
7-57	F	F	Me	2-Thiz-NH
7-58	F	F	Me	2,6DFP-NH

TABLE 7 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
7-59	F	F	Me	3FP-N-All
7-60	F	F	Me	3FP-N-Me
7-61	F	F	Me	ID
7-62	F	F	Me	4MB-NH
7-63	F	F	Me	1-Np-NH
7-64	F	F	Me	TP-NH
7-65	F	F	Me	2,5DFP-NH
7-66	F	F	Me	2-Pyr-NH
7-67	F	F	Me	cPn-NH
7-68	F	F	Me	2,4DFP-NH
7-69	F	F	Me	2,5DFP-NH
7-70	Cl	H	H	1-Pyrd
7-71	Cl	H	H	THQ
7-72	Cl	H	H	TAO
7-73	Cl	H	H	DMP-NH
7-74	Cl	H	H	4MP-NH
7-75	Cl	H	H	iBu-NH
7-76	Cl	H	H	TMP-NH
7-77	Cl	H	H	Bz-NH
7-78	Cl	H	H	1-Np-NH
7-79	Cl	H	H	cHx-NH
7-80	Cl	H	H	TM-NH
7-81	Cl	H	H	DB-NH
7-82	Cl	H	H	3FP-NH
7-83	Cl	H	H	2FP-NH
7-84	Cl	H	H	4PP-NH
7-85	Cl	H	H	ECM-NH
7-86	Cl	H	H	1AD-NH
7-87	Cl	H	H	MDP-NH

TABLE 7 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
7-88	Cℓ	H	H	2AD-NH
7-89	Cℓ	H	H	4FP-NH
7-90	Cℓ	H	H	3,5DFP-NH
7-91	Cℓ	H	H	2-Pym-NH
7-92	Cℓ	H	H	Et-NH
7-93	Cℓ	H	H	2-Fur-NH
7-94	Cℓ	H	H	2-Thiz-NH
7-95	Cℓ	H	H	2,6DFP-NH
7-96	Cℓ	H	H	3FP-N-All
7-97	Cℓ	H	H	3FP-N-Me
7-98	Cℓ	H	H	ID
7-99	Cℓ	H	H	4MB-NH
7-100	Cℓ	H	H	1-Np-NH
7-101	Cℓ	H	H	TP-NH
7-102	Cℓ	H	H	2,5DFP-NH
7-103	Cℓ	H	H	2-Pyr-NH
7-104	Cℓ	H	H	cPn-NH
7-105	Cℓ	H	H	2,4DFP-NH
7-106	Cℓ	H	Me	1-Pyrd
7-107	Cℓ	H	Me	THQ
7-108	Cℓ	H	Et	TAO
7-109	Cℓ	H	Pr	DMP-NH
7-110	Cℓ	H	Bu	4MP-NH
7-111	Cℓ	H	Pn	iBu-NH
7-112	Cℓ	H	Hx	TMP-NH
7-113	Cℓ	H	Et	DB-NH
7-114	Cℓ	H	Pr	3FP-NH
7-115	Cℓ	H	Bu	2FP-NH
7-116	Cℓ	H	Pn	4PP-NH

TABLE 7 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}
7-117	Cℓ	H	Hx	ECM-NH
7-118	Cℓ	H	Me	3,5DFP-NH
7-119	Cℓ	H	Me	2-Pym-NH
7-120	Cℓ	H	Me	Et-NH
7-121	Cℓ	H	Me	2-Fur-NH
7-122	Cℓ	H	Me	2-Thiz-NH
7-123	Cℓ	H	Me	2,6DFP-NH
7-124	Cℓ	H	Me	3FP-N-All
7-125	Cℓ	H	Me	3FP-N-Me
7-126	Cℓ	H	Me	ID
7-127	Cℓ	H	Me	4MB-NH
7-128	Cℓ	H	Me	1-Np-NH
7-129	Cℓ	H	Me	TP-NH
7-130	Cℓ	H	Me	2,5DFP-NH
7-131	Cℓ	H	Me	2-Pyr-NH
7-132	Cℓ	H	Me	cPn-NH
7-133	Cℓ	H	Me	2,4DFP-NH

TABLE 8

Cpd No.	X^1	X^2	R^1	R^{5a}	n	position of $(Me)_n$
8-1	F	F	H	1-Pyrd	1	2
8-2	F	F	H	THQ	2	2,2
8-3	F	F	H	TAO	3	2,2,5
8-4	F	F	H	DMP-NH	4	2,2,5,5
8-5	F	F	H	4MP-NH	2	2,5
8-6	F	F	H	iBu-NH	3	2,5,5
8-7	F	F	H	TMP-NH	2	5,5
8-8	F	F	H	Bz-NH	2	2,3
8-9	F	F	H	1-Np-NH	1	3
8-10	F	F	H	cHx-NH	3	2,2,3
8-11	F	F	H	TM-NH	4	2,2,3,3
8-12	F	F	H	DB-NH	4	2,3,5,7
8-13	Cl	H	H	1-Pyrd	1	2
8-14	Cl	H	H	THQ	2	2,2
8-15	Cl	H	H	TAO	3	2,2,5
8-16	Cl	H	H	DMP-NH	4	2,2,5,5
8-17	Cl	H	H	4MP-NH	2	2,5
8-18	Cl	H	H	iBu-NH	3	2,5,5
8-19	Cl	H	H	TMP-NH	2	5,5
8-20	Cl	H	H	Bz-NH	2	2,3
8-21	Cl	H	H	1-Np-NH	1	3
8-22	Cl	H	H	cHx-NH	3	2,2,3
8-23	Cl	H	H	TM-NH	4	2,2,3,3
8-24	Cl	H	H	DB-NH	4	2,3,5,7
8-25	F	Cl	H	1-Pyrd	1	2
8-26	F	Cl	H	THQ	2	2,2
8-27	F	Br	H	TAO	3	2,2,5
8-28	F	Cl	H	DMP-NH	4	2,2,5,5
8-29	F	H	H	4MP-NH	2	2,5

TABLE 8 (cont)

Cpd No.	X^1	X^2	R^1	R^{5a}	n	position of $(Me)_n$
8-30	F	H	H	iBu-NH	3	2,5,5
8-31	F	Cℓ	H	TMP-NH	2	5,5
8-32	F	Br	H	Bz-NH	2	2,3
8-33	F	H	H	1-Np-NH	1	3
8-34	F	Cℓ	H	cHx-NH	3	2,2,3
8-35	F	Br	H	TM-NH	4	2,2,3,3
8-36	F	H	H	DB-NH	4	2,3,5,7
8-37	Cℓ	Cℓ	H	1-Pyrd	1	2
8-38	Cℓ	Cℓ	H	THQ	2	2,2
8-39	Cℓ	Br	H	TAO	3	2,2,5
8-40	Cℓ	Cℓ	H	DMP-NH	4	2,2,5,5
8-41	Cℓ	Cℓ	H	4MP-NH	2	2,5
8-42	Cℓ	Br	H	iBu-NH	3	2,5,5
8-43	Cℓ	Cℓ	H	TMP-NH	2	5,5
8-44	Cℓ	Cℓ	H	Bz-NH	2	2,3
8-45	Cℓ	Br	H	1-Np-NH	1	3
8-46	Cℓ	Cℓ	H	cHx-NH	3	2,2,3
8-47	Cℓ	Cℓ	H	TM-NH	4	2,2,3,3
8-48	Cℓ	Cℓ	H	DB-NH	4	2,3,5,7
8-49	F	F	Et	2-Thiz-NH	2	2,2
8-50	F	F	Me	2,6DFP-NH	2	2,3
8-51	F	F	Et	3FP-N-All	3	2,2,3
8-52	F	F	Me	3FP-N-Me	4	2,2,3,3
8-53	Cℓ	H	Et	4MB-NH	1	5
8-54	F	H	Me	2,5DFP-NH	3	2,3,3
8-55	Cℓ	Cℓ	Et	2-Pyr-NH	3	2,3,5
8-56	F	F	H	3FP-NH	1	2

TABLE 9

Cpd. No.	X^1	X^2	R^1	R^{5a}	R^{6a}	R^{8a}	R^{10a}
9-1	F	F	H	3FP-NH	O	H,H	H,H
9-2	F	F	H	2FP-NH	H,H	O	H,H
9-3	F	F	H	4PP-NH	O	O	H,H
9-4	F	F	H	ECM-NH	Me,H	O	H,H
9-5	F	F	H	1AD-NH	Me,H	O	Me,H
9-6	Cl	H	H	3FP-NH	O	H,H	H,H
9-7	Cl	H	H	2FP-NH	H,H	O	H,H
9-8	Cl	H	H	4PP-NH	O	O	H,H
9-9	Cl	H	H	ECM-NH	Me,H	O	H,H
9-10	Cl	H	H	1AD-NH	Me,H	O	Me,H
9-11	F	Cl	H	3FP-NH	O	H,H	H,H
9-12	F	H	H	2FP-NH	H,H	O	H,H
9-13	F	H	H	4PP-NH	O	O	H,H
9-14	F	H	H	ECM-NH	Me,H	O	H,H
9-15	F	Cl	H	1AD-NH	Me,H	O	Me,H
9-16	F	F	Me	2-Fur-NH	Et,H	H,H	H,H
9-17	F	F	Et	ID	Et,H	H,H	Me,H
9-18	Cl	H	Me	1-Np-NH	H,H	H,H	Pr,Me
9-19	Cl	H	Me	TP-NH	Me,Me	H,H	Et,Me
9-20	F	H	Et	cPn-NH	Et,H	H,H	H,H
9-21	Cl	H	Me	2,4DPP-NH	Et,H	Et,H	H,H

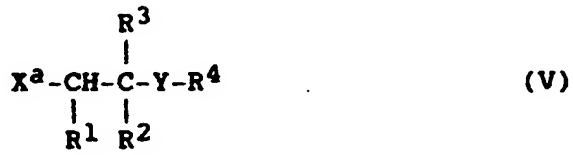
Of the compounds listed above, the following are preferred, that is to say Compounds No. 1-1, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-21, 1-26, 1-27, 1-28, 1-29, 1-36, 1-37, 1-39, 1-40, 1-41, 1-42, 1-44, 1-48, 1-49, 1-53, 1-54, 1-55, 1-56, 1-57, 1-59, 1-66, 1-69, 1-75, 1-76, 1-77, 1-81, 1-91, 1-92, 1-93, 1-102, 1-105, 1-108, 1-109, 1-113, 1-119, 1-120, 1-121, 2-1, 2-2, 2-5, 2-6, 3-1, 2-7, 2-8, 2-9, 2-10, 2-11, 2-12, 2-13, 2-14, 2-15, 2-16, 2-17, 2-19, 2-21, 2-22, 2-26, 2-29, 2-35, 2-38, 2-41, 2-47, 2-50, 2-53, 2-59, 2-61, 2-62, 2-63, 2-64, 2-65, 3-2, 3-5, 3-8, 3-9, 3-10, 3-11, 4-1, 4-3, 6-1, 7-1, 7-2, 7-3, 7-5, 7-6, 7-7, 7-8, 7-10, 7-11, 7-12, 7-13, 7-14, 7-15, 7-16, 7-17, 7-18, 7-26, 7-27, 7-28, 7-30, 7-38, 7-40, 7-41, 7-44, 7-45, 7-47, 7-52, 7-59, 7-60, 7-61, 7-63, 7-71, 7-74, 7-80, 7-82, 7-86, 7-96, 7-97, 7-98, 7-107, 7-110, 7-114, 7-124, 7-125, 7-126, 8-2, 8-5, 8-11, 8-14, 8-17, 8-23, 8-24, 8-26, 8-29, 8-35, 8-36, 8-38, 8-41, 8-48, 8-51, 8-52, 9-1, 9-5, 9-15 and 9-17. Of these, the more preferred compounds are Compounds No. 1-5, 1-7, 1-11, 1-12, 1-13, 1-26, 1-27, 1-28, 1-37, 1-44, 1-48, 1-69, 1-75, 1-77, 2-5, 2-7, 2-8, 2-11, 2-12, 2-19, 2-21, 2-62, 7-5, 7-11, 7-12, 7-13, 7-17, 7-30,

7-38, 7-45 and 7-52. The most preferred compounds are:
1-11. 1-[Bis(4-fluorophenyl)methyl]-4-(2,4,6-trimethylphenylcarbamoylmethyl)piperazine;
1-12. 1-[Bis(4-fluorophenyl)methyl]-4-(1,1-dimethylbenzylcarbamoylmethyl)piperazine;
1-13. 1-[Bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine;
1-27. 1-[Bis(4-fluorophenyl)methyl]-4-[N-allyl-N-(3-fluorophenyl)carbamoylmethyl]piperazine;
1-37. 1-[Bis(4-fluorophenyl)methyl]-4-[1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)ethyl]piperazine;
1-44. 1-[Bis(4-fluorophenyl)methyl]-4-[1-(3-fluorophenylcarbamoyl)ethyl]piperazine;
1-69. 1-(4-Chlorobenzhydryl)-4-(4-methoxyphenylcarbamoylmethyl)piperazine;
1-75. 1-(4-Chlorobenzhydryl)-4-(2,4,6-trimethylphenylcarbamoylmethyl)piperazine;
2-7. 1-[Bis(4-fluorophenyl)methyl]-4-[(4-methoxyphenyl)carbamoylmethyl]-2,5-dimethylpiperazine;
2-11. 1-[Bis(4-fluorophenyl)methyl]-4-[(2,4,6-trimethylphenyl)carbamoylmethyl]-3-methylpiperazine;
2-19. 1-[Bis(4-fluorophenyl)methyl]-4-[(3-fluorophenyl)carbamoylmethyl]-3,3-dimethylpiperazine;
7-52. 1-[Bis(4-fluorophenyl)methyl]-4-[1-(1-adamantylcarbamoyl)ethyl]homopiperazine;
and pharmaceutically acceptable salts of the above compounds, especially the hydrochlorides and maleates thereof.

The compounds of the present invention can be prepared by reacting a nitrogen-containing heterocyclic compound of formula (IV):

A - M - H (IV)

(in which A and M are as defined above) or an active derivative thereof with a substituted alkyl halide compound of formula (V):



(V)

(in which R^1, R^2, R^3 and R^4 are as defined above, and X^a represents a halogen atom, a carboxylic acyloxy group or a sulphonyloxy group).

Where X^a represents a halogen atom, this is preferably a chlorine, bromine or iodine atom. Where X^a represents a carboxylic acyloxy group, this is preferably an aliphatic carboxylic acyloxy group and more preferably a fatty acid acyloxy group, particularly a halogenated acetoxy group, such as a trifluoroacetoxy, chloroacetoxy or trichloroacetoxy group. Where X^a represents a sulphonyloxy group, this is preferably: a lower alkanesulphonyloxy group, such as a methanesulphonyloxy or ethanesulphonyloxy group; a halogenated lower alkanesulphonyloxy group, such as a trifluoromethanesulphonyloxy, trichloromethanesulphonyloxy or pentafluoroethanesulphonyloxy group; or an arylsulphonyloxy group, such as a toluenesulphonyloxy (e.g. p-toluenesulphonyloxy) or benzenesulphonyloxy group.

The reaction of the nitrogen-containing heterocyclic compound of formula (IV) with the substituted alkyl halide of formula (V) may be effected in the presence or absence of a solvent and in the presence or absence of a base.

Where a solvent is employed, its nature is not critical, provided that it has no adverse effect on the reaction, and any solvent conventionally used for reactions of this type may equally be employed here. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ketones, such as acetone; ethers, such as diethyl ether, dimethoxyethane, diethylene glycol dimethyl ether or tetrahydrofuran; amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and mixtures of any two or more of these solvents. The most preferred solvents are the ethers and the amides.

Equally, where a base is employed, its nature is not critical to the invention, and any base conventionally employed in alkylation reactions of this type may be used in this reaction. Examples of suitable bases include: inorganic bases, such as the alkali metal carbonates (e.g. sodium carbonate or potassium carbonate), the alkali metal bicarbonates (e.g. sodium bicarbonate or potassium bicarbonate) and the alkali metal hydrides (e.g. lithium hydride, sodium hydride or potassium hydride); and organic bases, especially tertiary amines such as triethylamine, diisopropylethylamine, pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene and 1,8-diazabicyclo[5.4.0]undec-7-ene.

The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. However, we generally find it convenient to carry out the reaction at a temperature of from −78°C to +200°C, and more preferably from 0°C to 140°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature, the nature of the starting materials, the presence or absence of the solvent, the nature of the solvent (if used), the presence or absence of the base and the nature of the base (if used), but a period of from 2 hours to 2 days will normally suffice.

If desired, in the resulting compound of formula (I), where one or both of R^4 and R^5 represents a hydrogen atom, the compound may be reacted with an appropriate reagent to introduce an alkyl, aryl, aralkyl, aromatic heterocyclic or alkenyl group on the nitrogen atom included in the definition of $-Y-R^4$.

This reaction may be effected by reacting the compound of formula (I) where one or both of R^4 and R^5 represents a hydrogen atom with a compound of formula $R^{4'}-X^a$ or $R^{5'}-X^a$ (in which X^a is as defined above, and $R^{4'}$ and $R^{5'}$ are the same or different and each represents an alkyl, aryl, aralkyl, aromatic heterocyclic or alkenyl group, as included in the definitions of R^4 and R^5). The reaction may be effected in the presence or absence of a solvent and is preferably effected in the presence of a base.

Where a solvent is employed, its nature is not critical, provided that it has no adverse effect on the reaction, and any solvent conventionally used for reactions of this type may equally be employed here. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ketones, such as acetone; ethers, such as diethyl ether, dimethoxyethane, diethylene glycol dimethyl ether or tetrahydrofuran; amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and mixtures of any two or more of these solvents. Of these, the ethers and amides are the preferred solvents.

There is equally no restriction on the nature of the base to be employed, and any base conventionally employed in alkylation and other reactions of this type may be used in this reaction. Examples of suitable bases include: inorganic bases, such as the alkali metal carbonates (e.g. sodium carbonate or potassium carbonate), the alkali metal bicarbonates (e.g. sodium bicarbonate or potassium bicarbonate), the alkali metal hydrides (e.g. lithium hydride, sodium hydride or potassium hydride) and the alkali metal hydroxides (e.g. sodium hydroxide or potassium hydroxide); organic bases, especially tertiary amines, such as triethylamine, diisopropylethylamine, pyridine, 1,5-diazabicyclo-[4.3.0]non-5-ene and 1,8-diazabicyclo[5.4.0]undec-7-ene; and basic organic metal compounds, such as butyllithium or lithium diisopropylamide.

The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. However, we generally find it convenient to carry out the reaction at a temperature of from −78°C to +100°C, and more preferably from −10°C to +30°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature, the nature of the starting materials, the presence or absence of the solvent, the nature of the solvent (if used), the presence or absence of the base and the nature of the base (if used), but a period of from 2 hours to 2 days will normally suffice.

The compounds of formula (IV) used as the starting materials may be obtained commercially or may be synthesised by the method described in J. Amer. Chem. Soc., 62, 1202 (1940) or in Japanese Patent Publication No. 46-24024 (1971), or they may be obtained by reduction of a compound thus synthesized.

BIOLOGICAL ACTIVITY

The compounds of the present invention have an excellent blocking effect on the entry of calcium into body cells and can thus offer significant protection against the adverse effects of cellular calcium overload; for example, they offer substantial protection against the lethal effects of low oxygen levels in the blood (especially for the brain) and can, therefore, be used to improve the condition of patients suffering from vascular disorders. Also, they have demonstrated a remarkably low toxicity, in contrast to the prior art compounds used for these purposes.

Calcium Entry Blocking Effect

This test was carried out according to the method of J. Booher [Neurobiology, 2, 97 - 105 (1972)].

The brain was harvested from rats one day after birth and unravelled through a nylon mesh. The unravelled brain cells were incubated in a plastic dish with a diameter of 35 mm, using as culture medium Dulbeccos Modified Eagle Medium (DMEM) containing 20 - 50% by weight of fetal calf serum. After the cells had been cultivated for 3 weeks, the glial cells were washed with DMEM and then incubated for 90

minutes with DMEM containing 20μM of A23187 (a calcium - ionophore compound) and the test compound. At the end of this time, the liquid medium was removed, and the dead cells were stained with 0.04% Trypan Blue. They were then examined under a microscope to determine the number of dead cells. [Science, 206, 700 (1979), F.A.X. Shanne et al.].

The suppressive rate was calculated as :

$$\frac{N_o - N_t}{N_o}$$

where N_o is the number of cells killed by A23187 alone and N_t is the number of cells killed by A23187 plus the test compound. The results are shown in Table 11. In this Table, as well as in Table 12, the compounds of the invention are identified by the numbers assigned to them in foregoing Tables 1 to 10.

Table 11

Compound No.	Concentration (μg/mℓ)	Suppressive Rate (%)
1-13	5	79
1-48	5	87
1-75	5	78
2-2	5	81
2-7	5	74
Flunarizine	5	53
Cinepazide	5	6

Protection Against Lethal Effects Of Low Atmospheric Oxygen Levels

Following an intraperitoneal injection of the test compound into male mice of the ddy strain, aged from 5 to 6 weeks, the mice were placed in a plastic box which was then filled with 96% nitrogen - 4% oxygen by volume, to measure the time required until death. As shown in Table 12, the compounds of the present invention were found to prolong the time until death.

Table 12

Compound No.	Dose (mg/kg)	Prolongation Rate (%)
1-75	30	93
Flunarizine	100	-29
Cinepazide	100	-11

It can be seen from the results reported in Tables 11 and 12 that the compounds of the present invention are significantly better than flunarizine and cinepazide as calcium entry blockers and are very substantially better than these prior art compounds at protecting against the lethal effects of low oxygen levels. Accordingly, the compounds of the present invention may be expected to be of considerable value in the treatment of vascular disorders, especially cerebral vascular disorders, and most particularly those arising from ischaemic effects.

The compounds of the present invention may be administered by any convenient route, as is well known in this field, and the form of pharmaceutical preparation will be chosen having regard to the chosen route of administration. For example, for oral administration, the compounds may be administered in the form of tablets, capsules, granules, powders or syrups. For parenteral administration, they may be formulated as injections or suppositories. These preparations may be produced in a conventional manner using such common additives, adjuvants, diluents and carriers as excipients, binders, disintegrators, lubricants, stabilizers, corrigents and the like. The recommended dosage will, of course, vary, depending upon many factors, including the age and body weight of the patient as well as the nature, symptoms and severity of the disease. However, for an adult human patient, a daily dose of from 1 mg to 100 mg per kg body weight (which may be administered in a single dose or in divided doses) is suggested.

The preparation of various of the compounds of the present invention is further illustrated in the following non-limiting Examples. Again, the compounds of the present invention are identified by the numbers assigned to them in Tables 1 - 10.

EXAMPLE 1

1-[Bis(4-fluorophenyl)methyl]-4-(1-naphthylcarbamoylmethyl)piperazine and its hydrochloride (Compound No. 1-9)

A mixture of 290 mg of 1-[bis(4-fluorophenyl)methyl]piperazine and 400 mg of N-(1-naphthyl)-chloroacetamide was dissolved in 10 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide. 1.2 g of anhydrous potassium carbonate was then added to the solution, after which the reaction mixture was stirred for 15 hours at 25°C and then diluted with ethyl acetate. The organic layer was separated and washed three times with water and then dried over anhydrous magnesium sulphate. The solvent was then evaporated off under reduced pressure. The resulting residue was subjected to silica gel thin layer chromatography using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to afford 430 mg of 1-[bis(4-fluorophenyl)methyl]-4-(1-naphthylcarbamoyl-methyl)piperazine, melting at 173°C.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

2.3 - 2.9 (8H);
3.25 (2H, singlet);
4.30 (1H, singlet);
6.8 - 8.4 (15H);
9.95 (1H, singlet).

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:

3270, 1690, 1600,

Mass Spectrum (m/e): 471, 301, 203.

300 mg of this 1-[bis(4-fluorophenyl)methyl]-4-(1-naphthylcarbamoylmethyl)piperazine were dissolved in 5 ml of acetone, and then a 4.92 M ethanolic solution of hydrogen chloride were added dropwise, to precipitate 310 mg of the title dihydrochloride, melting at 165 - 172°C,

Elemental analysis:			
Calculated for $C_{29}H_{27}N_3OF_2 . 2HCl$:	C, 63.97%;	H, 5.37%;	N, 7.72%.
Found:	C, 63,75%;	H, 5,40%;	N, 7,75%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CD_3OD) δ ppm:

3.18 - 3.29 (4H);
3.68 - 3.80 (4H);
4.43 (2H, singlet);
5.23 (1H, singlet);

7.1 - 8.1 (15H).

EXAMPLE 2

1-(4-Chlorobenzhydryl)-4-(2,4,6-trimethylphenylcarbamoylmethyl)piperazine hydrochloride (Compound No. 1-75)

2 g of anhydrous potassium carbonate were added to a mixture of 192.6 mg of 1-(4-chlorobenzhydryl)piperazine and 142.7 mg of N-(2,4,6-trimethylphenyl)chloroacetamide dissolved in 20 ml of N,N-dimethylformamide, and the reaction mixture was then stirred at 80°C for 7.5 hours. At the end of this time, ethyl acetate was added to the mixture, and the organic layer was separated. The separated organic layer was washed three times with water, and then the solvent was evaporated off under reduced pressure. The residue was subjected to silica gel thin layer chromatography using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to afford a purified 1-(4-chlorobenzhydryl)-4-(2,4,6-trimethylphenylcarbamoylmethyl)piperazine.

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:

3280, 2910, 2810, 1715, 1700, 1610, 1600, 1510.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

2.10 (6H, singlet),
2.21 (3H, singlet);
1.9 - 2.9 (8H, multiplet);
3.12 (2H, singlet);
4.21 (1H, singlet);
7.1 - 7.7 (9H, multiplet);
8.56 (1H, broad singlet).

Mass Spectrum (m/e): 461, 201.

The whole of this purified 1-(4-chlorobenzhydryl)-4-(2,4,6-trimethylphenylcarbamoylmethyl)-piperazine was dissolved in 5 ml of ethanol and mixed with an excess of a 4.92 M ethanolic solution of hydrogen chloride. The resulting hydrochloride was crystallized by the addition of diethyl ether, to afford 207.3 mg of the crude dihydrochloride of the title compound as crystals, melting at 140 - 145°C.

This compound was recrystallized from a mixture of ethanol and diethyl ether, to give the monohydrate of the title compound, melting at 149.5 - 150.5°C.

Elemental Analysis:			
Calculated for $C_{28}H_{32}N_3OCl.2HCl.H_2O$:	C, 60.82%;	H, 6.56%;	N, 7.60%.
Found:	C, 61.32%;	H, 6.82%;	N, 7.53%.

Nuclear Magnetic Resonance Spectrum (270MHz, CD_3OD) δ ppm:

2.16 (6H, singlet);
2.25 (3H, singlet);
3.30 (4H, broad singlet);
3.65 (4H, broad singlet);
4.35 (2H, singlet);
5.30 (1H, singlet);
6.90 (2H, singlet);
7.3 - 7.9 (9H, multiplet).

EXAMPLE 3

1-[Bis(4-fluorophenyl)methyl]-4-[(2,4,6-trimethylphenyl)carbamoylmethyl]-3-methylpiperazine hydrochloride (Compound No. 2-11)

A mixture of 300 mg of 1-[bis(4-fluorophenyl)methyl]-3-methylpiperazine and 252 mg of N-(2,4,6-trimethylphenyl)chloroacetamide was dissolved in 20 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide. 100 mg of anhydrous potassium carbonate were then added to the solution, and the resulting reaction mixture was stirred at 70°C for 3 hours, after which ethyl acetate was added to it and the organic layer was separated. The separated organic layer was washed three times

with water, and then dried over anhydrous magnesium sulphate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was subjected to silica gel thin layer chromatography using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to afford a purified 1-[bis(4-fluorophenyl)methyl]-4-[(2,4,6-trimethylphenyl)-carbamoylmethyl]-3-methylpiperazine.

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:

3275, 1680, 1600, 1500, 1220, 1150, 1040.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

1.08 (3H, doublet, J = 6 Hz);
2.14 (6H, singlet);
2.22 (3H, singlet);
1.55 - 2.95 (7H, multiplet);
2.85 (1H, doublet, J = 18 Hz);
3.52 (1H, doublet, J = 18 Hz);
4.18 (1H, singlet);
6.65 - 7.55 (10H, multiplet).

Mass Spectrum (m/e): 477, 203.

This purified 1-[bis(4-fluorophenyl)methyl]-4-[(2,4,6-trimethylphenyl)carbamoylmethyl]-3-methylpiperazine was dissolved in 3 ml of ethanol, and the resulting solution was mixed with an excess of a 4.92 M ethanolic solution of hydrogen chloride. Diethyl ether was then added, to afford 255 mg of the crystalline title dihydrochloride.

EXAMPLE 4

1-[Bis(4-fluorophenyl)methyl]-4-[(4-methoxyphenyl)carbamoylmethyl]-2,5-dimethylpiperazine hydrochloride (Compound No. 2-7)

A mixture of 416 mg of 1-[bis(4-fluorophenyl)methyl]-2,5-dimethylpiperazine and 316 mg of N-(4-methoxyphenyl)chloroacetamide was dissolved in 5 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide. 365 mg of anhydrous potassium carbonate were then added to the solution, and the reaction mixture was stirred at 80°C for 5 hours. At the end of this time, ethyl acetate was added to the mixture, and the organic layer was separated. The organic layer was washed three times with water, and then dried over anhydrous magnesium sulphate. The solvent was removed by evaporation under reduced pressure, and the residue was subjected to silica gel thin layer chromatography using a 2 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to afford a purified 1-[bis(4-fluorophenyl)methyl]-4-[(4-methoxyphenyl)carbamoylmethyl]-2,5-dimethylpiperazine, melting at 131°C.

Elemental analysis:			
Calculated for $C_{28}H_{31}N_3O_2F_2$:	C, 70.13%;	H, 6.52%;	N, 8.76%.
Found:	C, 69.93%;	H, 6.53%;	N, 8.78%.

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:

3350, 1670, 1520, 1505, 1245.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

1.04 (3H, doublet, J = 6 Hz);
1.18 (3H, doublet, J = 6 Hz);
1.8 - 2.93 (6H, multiplet);
3.12 (2H, doublet, J = 18 Hz);
3.76 (3H, singlet);
5.50 (1H, singlet);
6.78 - 7.52 (12H, multiplet);
9.07 (1H, broad singlet).

Mass Spectrum (m/e): 479, 203.

This purified 1-[bis(4-fluorophenyl)methyl]-4-[(4-methoxyphenyl)carbamoylmethyl]-2,5-dimethylpiperazine was dissolved in 30 ml of diethyl ether. An excess of a 4.92 M ethanolic solution of hydrogen chloride was added to the solution to yield a white precipitate, which was collected by filtration, to

afford 532 mg of the monohydrate of the title compound, melting at 141 °C.

Elemental Analysis:			
Calculated for $C_{28}H_{31}N_3O_2F_2.2HCl.H_2O$:	C, 58.95%;	H, 6.18%;	N, 7.36%.
Found:	C, 58.41%;	H, 6.21%;	N, 7.32%.

1 g of this compound was recrystallized by dissolving it in 5 ml of ethanol and then adding 5 ml of diethyl ether, to give 950 mg of the corresponding anhydride, melting at 160 - 170 °C.

Elemental Analysis:			
Calculated for $C_{28}H_{31}N_3O_2F_2$. 2HCl:	C, 60.87%;	H, 6.02%;	N, 7.61%.
Found:	C, 60.49%;	H, 6.07%;	N, 7.47%.

Nuclear Magnetic Resonance Spectrum (270MHz, CD_3OD) δ ppm:
1.36 (3H, doublet, J = 6.2 Hz);
1.43 (3H, doublet, J = 5.9 Hz);
3.15 - 4.30 (6H, multiplet);
4.09 (2H, doublet, J = 15.8 Hz);
3.76 (3H, singlet);
5.88 (1H, singlet);
6.86 - 7.69 (12H, multiplet).
Infrared Absorption Spectrum (Nujol - trade mark) ν_{max} cm^{-1}:
3410, 1696, 1609, 1512, 1417.
Ultraviolet Absorption Spectrum (ethanol) λ_{max}:
253 nm (ϵ = 17,800).

EXAMPLE 5

1-[Bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine hydrochloride or maleate (Compound No. 1-13)

A mixture of 300 mg of 1-[bis(4-fluorophenyl)methyl]piperazine and 234 mg of N-(3-fluorophenyl)chloroacetamide was dissolved in 20 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide, and 400 mg of anhydrous potassium carbonate were added to the solution. The reaction mixture was then stirred at 70 °C for 2 hours, after which ethyl acetate was added to it and the organic layer was separated. The separated organic layer was washed three times with water, and then dried over anhydrous magnesium sulphate, after which the solvent was removed by evaporation under reduced pressure. The residue was subjected to silica gel thin layer chromatography using a 2 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to give a purified 1-[bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.18 - 3.88 (8H, multiplet);
3.1 (2H, singlet);
4.22 (1H, singlet);
6.58 - 7.78 (12H, multiplet);
9.23 (1H, singlet).
Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1520, 1440, 1330, 1220.
Mass Spectrum (m/e): 437, 203.
The whole of the 1-[bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine obtained as described above was then dissolved in 3 ml of ethanol. An excess of a 4.92 M ethanolic solution of hydrogen chloride was added to the solution, after which the resulting compound was crystallized by adding diethyl ether, to afford 244 mg of the title hydrochloride, melting at 145 - 154 °C.
Nuclear Magnetic Resonance Spectrum (270 MHz, CD_3OD) δ ppm:
3.47 (4H, broad singlet);

3.88 (4H, broad singlet);
4.32 (2H, singlet);
5.60 (1H, singlet);
6.8 - 7.9 (12 H).

The purified 1-[bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine obtained as described above was also dissolved in 3 ml of ethanol, and then an ethanolic solution containing one molar equivalent of maleic acid was added. The resulting product was crystallized by adding diethyl ether, to afford the maleate.

Nuclear Magnetic Resonance Spectrum (270 MHz, CD_3OD) δ ppm:
2.72 (4H);
3.35 (4H);
3.99 (2H, singlet);
4.52 (1H, singlet);
6.26 (2H, singlet);
6.8 - 6.9 (1H, multiplet);
7.0 - 7.2 (4H, multiplet);
7.2 - 7.4 (2H, multiplet);
7.4 - 7.6 (5H, multiplet).

EXAMPLE 6

1-[Bis(4-fluorophenyl)methyl]-4-[1-(1-adamantylcarbamoyl)ethyl]homopiperazine maleate (Compound No. 7-52)

A mixture of 300 mg of 1-[bis(4-fluorophenyl)methyl]homopiperazine and 300 mg of N-(1-adamantyl)-2-bromopropionamide was dissolved in 20 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide, and then 100 mg of anhydrous potassium carbonate were added to the resulting solution. The reaction mixture was stirred at 90°C for 2 hours, and then ethyl acetate was added, and the organic layer was separated. The separated organic layer was washed three times with water, and then dried over anhydrous magnesium sulphate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was subjected to silica gel thin layer chromatography, using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to give a purified 1-[bis(4-fluorophenyl)methyl]-4-[1-(1-adamantylcarbamoyl)ethyl]homopiperazine.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.15 (3H, doublet, J = 7 Hz);
1.45 - 2.3 (17H, multiplet);
2.4 - 2.9 (8H, multiplet);
3.15 (1H, quartet, J = 7 Hz);
4.6 (1H, singlet);
6.8 - 7.6 (8H, multiplet).

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1740, 1660, 1600, 1510, 1450, 1360, 1220.

Mass Spectrum (m/e): 507, 329, 203.

This purified product was dissolved in acetone, and the solution was mixed with 0.5 mole of maleic acid. The resulting salt was crystallized by adding diethyl ether to afford 100 mg of the title compound.

EXAMPLE 7

1-[Bis(4-fluorophenyl)methyl]-4-[1-(3-fluorophenylcarbamoyl)ethyl]piperazine hydrochloride (Compound No. 1-44)

A mixture of 300 mg of 1-[bis(4-fluorophenyl)methyl]piperazine and 256 mg of N-(3-fluorophenyl)-2-bromopropionamide was dissolved in 20 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide, and 100 mg of anhydrous potassium carbonate were added to the resulting solution. The reaction mixture was then stirred at 90°C for 2 hours. At the end of this time, ethyl acetate was added, and the organic layer was separated. The separated organic layer was washed three times with water, and then dried over anhydrous magnesium sulphate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was subjected to silica gel thin layer

chromatography using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to give 1-[bis(4-fluorophenyl)methyl]-4-[1-(3-fluorophenylcarbamoyl)ethyl]piperazine.

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:

3300, 1700, 1600, 1510, 1440, 1220, 1140.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

1.28 (3H, doublet, J = 7 Hz);
2.1 - 2.9 (8H, multiplet);
3.15 (1H, quartet, J = 7 Hz);
4.22 (1H, singlet);
6.5 - 7.5 (12H, multiplet);
9.4 (1H, singlet).

Mass Spectrum (m/e): 453, 203.

The product obtained as described above was dissolved in 3 ml of ethanol, and an excess of a 4.92 M ethanolic solution of hydrogen chloride was added to the solution. The resulting hydrochloride was then crystallized by adding diethyl ether, to afford 250 mg of the title compound.

EXAMPLE 8

1-[Bis(4-fluorophenyl)methyl]-4-[1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)ethyl]piperazine hydrochloride (Compound No. 1-37)

A mixture of 300 mg of 1-[bis(4-fluorophenyl)methyl]piperazine and 280 mg of N-(1,2,3,4-tetrahydro-1-quinolyl)-2-bromopropionamide was dissolved in 20 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide, and 100 mg of anhydrous potassium carbonate were added to the resulting solution. The solution was then stirred at 90°C for 2 hours, after which ethyl acetate was added, and the organic layer was separated. The organic layer was washed three times with water, and dried over anhydrous magnesium sulphate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was subjected to silica gel thin layer chromatography using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to give a purified 1-[bis(4-fluorophenyl)methyl]-4-[1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)ethyl]piperazine.

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:

1730, 1640, 1575, 1500.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

1.23 (3H, doublet, J = 7 Hz);
1.6 - 2.8 (12H, multiplet);
3.6 - 4.02 (4H, multiplet);
4.19 (1H, singlet);
6.8 - 7.48 (12H, multiplet).

Mass Spectrum (m/e): 475, 203.

The purified product obtained as described above was dissolved in 3 ml of ethanol, and an excess of a 4.92 M ethanolic solution of hydrogen chloride was added to the solution. The hydrochloride was crystallized by adding diethyl ether, to yield 265 mg of the title compound as the dihydrochloride.

EXAMPLE 9

1-[Bis(4-fluorophenyl)methyl]-4-[(3-fluorophenyl)carbamoylmethyl]-3,3-dimethylpiperazine hydrochloride (Compound No. 2-19)

A mixture of 283 mg of 1-[bis(4-fluorophenyl)methyl]-3,3-dimethylpiperazine and 204 mg of N-(3-fluorophenyl)chloroacetamide was dissolved in 20 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide, and 1 g of anhydrous potassium carbonate was added to the resulting solution. The reaction mixture was then stirred at 80°C for 16 hours, after which ethyl acetate was added, and the organic layer was separated. The organic layer was washed with water and dried over anhydrous magnesium sulphate. The solvent was then removed by evaporation under reduced pressure. The residue was subjected to silica gel thin layer chromatography using a 2 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to give a purified 1-[bis(4-fluorophenyl)methyl]-4-[(3-fluorophenyl)carbamoylmethyl]-3,3-dimethylpiperazine.

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:

3270, 2910, 1690, 1600, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.08 (6H, singlet);
2.0 - 2.9 (6H, multiplet);
3.10 (2H, singlet);
4.19 (1H, broad singlet);
6.5 - 7.8 (12H, multiplet);
9.54 (1H, broad singlet).
Mass Spectrum (m/e): 467, 203.

The purified product was dissolved in 30 ml of diethyl ether, and an excess of a 4.92 M ethanolic solution of hydrogen chloride was added to the solution. The resulting white precipitate was collected by filtration to afford 49.8 mg of the title compound dihydrochloride.

EXAMPLE 10

1-[Bis(4-fluorophenyl)methyl]-4-[N-allyl-N-(3-fluorophenyl)carbamoylmethyl]piperazine hydrochloride (Compound No. 1-27)

12.65 mg of sodium hydride were added at room temperature to a solution of 115 mg of 1-[bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine (prepared as described in Example 5) in 10 ml of a 1 : 1 by volume mixture of tetrahydrofuran and N,N-dimethylformamide, whilst stirring, over a period of 20 minutes. 31.6 mg of allyl bromide were then added to the reaction mixture, after which the mixture was stirred overnight and then mixed with ethyl acetate. It was then washed three times with water, and dried over anhydrous magnesium sulphate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was subjected to silica gel thin layer chromatography using a 1 : 1 by volume mixture of cyclohexane and ethyl acetate as the developing solvent, to give 40 mg of a purified 1-[bis(4-fluorophenyl)methyl]-4-[N-allyl-N-(3-fluorophenyl)carbamoylmethyl]piperazine.
Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1730, 1660, 1500, 1460.
Nuclear Magnetic Resonance Spectrum (60 MHz. $CDCl_3$) δ ppm:
2.1 - 2.7 (8H, multiplet);
2.91 (2H, singlet);
4.18 (2H, singlet);
4.29 (1H, singlet);
4.8 - 6.15 (3H, multiplet);
6.7 - 7.5 (12H, multiplet).
Mass Spectrum (m/e): 479, 203.

The purified product was dissolved in ethanol, and an excess of a 4.92 M ethanolic solution of hydrogen chloride was added to the solution. The resulting hydrochloride was crystallized by adding diethyl ether, to afford 27 mg of the title compound.

EXAMPLE 11

1-[Bis(4-fluorophenyl)methyl]-4-[(4-methoxyphenyl)carbamoylmethyl]-2,5-(trans)-dimethylpiperazinehydrochloride

A mixture of 5 g of 1-bis(4-fluorophenyl)methyl alcohol in 10 ml of concentrated hydrochloric acid was heated under reflux for 4 hours. At the end of this time, the reaction mixture was separated into two phases in situ, and the organic layer was distilled under reduced pressure [130 - 133°C/1.5 mmHg (~200 Pa)], to give 4.26 g of colourless 1-bis(4-fluorophenyl)methyl chloride. A mixture of the whole of this 1-bis(4-fluorophenyl)methyl chloride and 4.08 g (2 molar equivalents) of 2,5-(trans)dimethylpiperazine in 85 ml of toluene was then heated under reflux for 9 hours. At the end of this time, the reaction mixture was extracted with 2.6 M aqueous acetic acid, and the extract was adjusted to a basic pH by the addition of aqueous ammonia and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography, using a 10 : 1 by volume mixture of ethyl acetate and methanol as eluent, to give 3.96 g of 1-[bis(4-fluorophenyl)methyl]-2,5-(trans)-dimethylpiperazine, as crystals melting at 98°C.

Elemental analysis:			
Calculated for for $C_{19}H_{22}N_2F_2$:	C, 72.13%;	H, 7.09%;	N, 8.85%.
Found:	C, 71.93%;	H, 7.09%;	N, 8.83%.

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.93 (3H, doublet, J = 6 Hz);
1.15 (3H, doublet, J = 6 Hz);
2.12 - 3.02 (6H, multiplet);
5.33 (1H, singlet);
6.83 - 7.52 (8H, multiplet).
Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:
3320, 1600, 1504, 1222, 1150.

This was then treated as described in Example 4, to give the title compound having essentially the same properties as the product of Example 4.

EXAMPLES 12 to 91

The following compounds were also prepared using procedures similar to those described above in Examples 1 to 11. In the following description, the compounds of the present invention are identified by the numbers heretofore assigned to them in Tables 1 to 4 and 6 to 9:

Compound No. 1 - 1:

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.4 - 2.2 (4H, multiplet);
2.2 - 2.8 (8H, multiplet);
3.1 (2H, singlet);
3.2 - 3.8 (4H, multiplet);
4.25 (1H, singlet);
6.8 - 7.5 (8H, multiplet).
Mass Spectrum (m/e): 399, 203.

Compound No. 1 - 2:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1650, 1600, 1500, 1400, 1220, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.6 - 2.9 (12H, multiplet);
3.29 (2H, singlet);
3.75 (2H, triplet, J = 6 Hz);
4.2 (1H, singlet);
6.7 - 7.7 (12H, multiplet).
Mass Spectrum (m/e): 461, 203.

Compound No. 1 - 3:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1740, 1640, 1500, 1220, 1160.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.7 - 3.7 (28H, multiplet);
4.6 (1H, singlet);
6.7 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 481, 203.

Compound No. 1 - 4:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1690.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.2 - 2.8 (8H, multiplet);
3.1 (2H, singlet);
3.75 (6H, singlet);
4.25 (1H, singlet);
6.15 - 7.50 (11H, multiplet).
Mass Spectrum (m/e): 481, 203.

Compound No. 1 - 5:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3320, 1680, 1600, 1510, 1410, 1300, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.2 - 2.9 (8H, multiplet);
3.1 (2H, singlet);
3.72 (3H, singlet);
4.23 (1H, singlet);
6.7 - 7.6 (12H, multiplet);
8.94 (1H, singlet).
Mass Spectrum (m/e): 451, 301, 203.

Compound No. 1 - 6:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3400, 1680, 1600, 1510, 1300, 1220, 1160, 1016.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.9 (6H, doublet, J = 6 Hz);
1.3 - 2.0 (1H, multiplet);
2.2 - 2.8 (8H, multiplet);
3.0 (2H, singlet);
3.1 (2H, triplet, J = 6 Hz);
4.21 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 401, 301, 203.

Compound No. 1 - 7:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3400, 1680, 1600, 1500, 1450, 1410, 1220, 1130.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.3 - 2.8 (8H, multiplet);
3.1 (2H, singlet);
3.8 (3H, singlet);
3.85 (6H, singlet);
4.29 (1H, singlet);
6.8 - 7.5 (10H, multiplet);
9.03 (1H, singlet).
Mass Spectrum (m/e): 511, 301, 203.

Compound No. 1 - 8:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1650, 1600, 1490, 1440, 1205, 1140.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:

2.2 - 2.7 (8H, multiplet);
3.05 (2H, singlet);
4.2 (1H, singlet);
4.46 (2H, doublet, J = 5 Hz);
6.7 - 7.5 (13H, multiplet).
Mass Spectrum (m/e): 435, 301, 203.

Compound No. 1 - 10:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1670, 1600, 1500, 1220, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.6 - 2.1 (11H, multiplet);
2.2 - 2.8 (8H, multiplet);
3.0 (2H, singlet);
4.25 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 427, 203.

Compound No. 1 - 11:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3325, 1680, 1600, 1500, 1300, 1220, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.16 (6H, singlet);
1.23 (3H, singlet);
1.9 - 2.8 (8H, multiplet);
3.16 (2H, singlet);
4.26 (1H, singlet);
6.8 - 7.6 (10H, multiplet);
8.56 (1H, singlet).
Mass Spectrum (m/e): 463, 203.

Compound No. 1 - 12:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1670, 1600, 1500, 1220, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.66 (6H, singlet);
2.15 - 2.8 (8H, multiplet);
2.93 (2H, singlet);
4.2 (1H, singlet);
6.75 - 7.6 (13H, multiplet).
Mass Spectrum (m/e): 463, 301.

Compound No. 1 - 14:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1700, 1620, 1600, 1520, 1450, 1220, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.15 - 2.85 (8H, multiplet);
3.14 (2H, singlet);
4.23 (1H, singlet);
6.75 - 7.55 (11H, multiplet);
8.2 - 8.65 (1H, multiplet);
9.55 (1H, singlet).
Mass Spectrum (m/e): 439, 203.

Compound No. 1-15:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1600, 1510, 1420, 1220, 1160.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.0 (3H, triplet, J = 7 Hz);
1.4 - 2.1 (2H, multiplet);
2.2 - 2.9 (8H, multiplet);
3.1 (2H, singlet);
3.95 (2H, triplet, J = 6 Hz):
4.24 (1H, singlet);
6.7 - 7.6 (12H, multiplet);
8.91 (1H, singlet).
Mass Spectrum (m/e): 479, 203.

Compound No. 1-16:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3375, 1745, 1680, 1600, 1500, 1370, 1300, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.21 (3H, triplet, J = 7 Hz);
2.2 - 2.8 (8H, multiplet);
3.01 (2H, singlet);
4.0 (2H, doublet, J = 5 Hz);
4.15 (2H, quartet, J = 7 Hz);
4.2 (1H, singlet);
6.75 - 7.8 (9H, multiplet).
Mass Spectrum (m/e): 431, 203.

Compound No. 1-17:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3325, 1670, 1600, 1500, 1470, 1380, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.5 - 1.8 (6H, multiplet);
1.8 - 2.2 (9H, multiplet);
2.2 - 2.7 (8H, multiplet);
2.82 (2H, singlet);
4.15 (1H, singlet);
6.75 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 493, 290.

Compound No. 1-18:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1510, 1450, 1160, 1040.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.2 - 2.9 (8H, multiplet);
3.1 (2H, singlet);
4.26 (1H, singlet);
5.9 (2H, singlet);
6.7 - 7.7 (11H, multiplet);
9.01 (1H, singlet).
Mass Spectrum (m/e): 465.

Compound No. 1 - 19:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1660, 1600, 1500, 1300, 1220, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.5 - 2.1 (15H, multiplet);
2.2 - 2.8 (8H, multiplet);
3.03 (2H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 479.

Compound No. 1 - 20:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1510, 1410, 1300, 1210.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.2 - 2.9 (8H, multiplet);
3.1 (2H, singlet);
4.27 (1H, singlet);
6.8 - 7.8 (12H, multiplet);
9.14 (1H, singlet).

Compound No. 1 - 21:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 2840, 1700, 1625, 1605, 1530, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.2 - 2.9 (8H, multiplet);
3.10 (2H, singlet);
4.26 (1H, singlet);
6.2 - 7.6 (11H, multiplet);
9.28 (1H, broad singlet).
Mass Spectrum (m/e): 457, 203.

Compound No. 1 - 26:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1700, 1600, 1510, 1460, 1220, 1160, 1050.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.2 - 2.9 (8H, multiplet);
3.18 (2H, singlet);
4.22 (1H, singlet);
6.7 - 7.6 (8H, multiplet);
8.7 (1H, singlet).
Mass Spectrum (m/e): 457, 203.

Compound No. 1 - 36:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1650, 1600, 1500, 1440, 1230, 1160, 1020, 830.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.25 (3H, doublet, J = 6 Hz);
2.1 - 2.9 (8H, multiplet);
3.47 (1H, quartet, J = 6 Hz);
4.19 (1H, singlet);
4.7 (1H, doublet, J = 14 Hz);
4.78 (2H, singlet);
5.21 (1H, doublet, J = 14 Hz);

6.7 - 7.6 (12H, multiplet).
Mass Spectrum (m/e): 361, 203.

Compound No. 1-39:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1730, 1690, 1600, 1530, 1500, 1460, 1420, 1160.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.28 (3H, doublet, J = 6 Hz);
2.2 - 2.8 (8H, multiplet);
3.18 (1H, quartet, J = 6 Hz);
3.75 (6H, singlet);
4.2 (1H, singlet);
6.6 - 7.5 (11H, multiplet);
9.22 (1H, singlet).
Mass Spectrum (m/e): 495, 203.

Compound No. 1-41:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1600, 1500, 1220, 1160.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.39 (3H, doublet, J = 6 Hz);
2.28 - 2.98 (8H, multiplet);
3.33 (1H, quartet, J = 6 Hz);
4.3 (1H, singlet);
6.78 - 8.38 (15H, multiplet);
10.05 (1H, singlet).
Mass Spectrum (m/e): 485, 203.

Compound No. 1-42:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1500, 1330, 1300, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.33 (3H, doublet, J = 7 Hz);
2.13 (6H, singlet);
2.25 (3H, singlet);
1.88 - 2.98 (8H, multiplet);
3.18 (1H, quartet, J = 7 Hz);
4.26 (1H, singlet);
6.78 - 7.58 (10H, multiplet);
8.58 (1H, singlet).
Mass Spectrum (m/e): 477, 203.

Compound No. 1-48:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1740, 1670, 1600, 1500, 1450, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.15 (3H, doublet, J = 8 Hz);
1.5 - 1.8 (6H, multiplet);
1.8 - 2.2 (9H, multiplet);
2.2 - 2.7 (8H, multiplet);
2.89 (1H, quartet, J = 8 Hz);
4.2 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 493, 315.

Compound No. 1 - 49:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1700, 1600.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.29 (3H, doublet, J = 6 Hz);
2.3 - 2.8 (8H, multiplet);
3.2 (1H, quartet, J = 6 Hz);
4.25 (1H, singlet);
6.3 - 7.5 (11H, multiplet).
Mass Spectrum (m/e): 471, 315, 203.

Compound No. 1 - 53:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 2950, 1690, 1600, 1530, 1500, 1320, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.3 (3H, doublet, J = 7 Hz);
2.2 - 2.8 (8H, multiplet);
3.34 (1H, quartet, J = 7 Hz);
4.2 (1H, singlet);
6.8 - 7.6 (10H, multiplet).
Mass Spectrum (m/e): 442, 315, 203.

Compound No. 1 - 54:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1700, 1600, 1510, 1460, 1220, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.28 (3H, doublet, J = 7 Hz);
2.2 - 3.0 (8H, multiplet);
3.26 (1H, quartet, J = 7 Hz);
4.2 (1H, singlet);
6.6 - 7.6 (11H, multiplet);
8.8 (1H, singlet).
Mass Spectrum (m/e): 471, 203.

Compound No. 1 - 56:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3475, 1660, 1600, 1500, 1220, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.1 - 2.7 (8H, multiplet);
2.98 (2H, singlet);
3.23 (3H, singlet);
4.2 (1H, singlet);
6.8 - 7.7 (12H, multiplet).
Mass Spectrum (m/e): 453, 203.

Compound No. 1 - 69:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3310, 2940, 2800, 1685, 1595, 1515, 1495.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.1 - 2.8 (8H, multiplet);
3.07 (2H, singlet);
3.71 (6H singlet);
4.22 (1H, singlet);

6.6 - 7.7 (13H, multiplet);
9.00 (1H, broad singlet).
Mass Spectrum (m/e): 449, 201.

Compound No. 1-77:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3300, 3000, 2840, 1690, 1618, 1525, 1497.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.1 - 2.9 (8H, multiplet);
3.07 (2H, singlet);
4.21 (1H singlet);
6.5 - 7.8 (13H, multiplet);
9.24 (1H, broad singlet).
Mass Spectrum (m/e): 437, 201.

Compound No. 2-1:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3300, 2960, 2830, 1685, 1615, 1600, 1520, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.7 - 2.6 (9H, multiplet);
2.1 - 3.3 (4H, multiplet);
3.2 - 3.8 (2H, multiplet);
4.3 - 4.9 (1H, multiplet);
5.12 (1H, singlet);
6.0 - 6.7 (2H, multiplet);
6.7 - 7.7 (10H, multiplet);
9.57 (1H, broad singlet).
Mass Spectrum (m/e): 481, 203.

Compound No. 2-2:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 2975, 2925, 2830, 1680, 1605, 1500.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.7 - 1.9 (19H, multiplet);
2.12 (6H, singlet);
2.23 (3H, singlet);
2.0 - 3.3 (6H, multiplet);
3.3 - 4.0 (1H, multiplet);
5.15 (1H, singlet);
6.7 - 7.7 (12H, multiplet);
6.55 (0.5H, broad singlet);
6.87 (0.5H, broad singlet).
Mass Spectrum (m/e): 505, 343, 203.

Compound No. 2-5:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3300, 2910, 1665, 1605, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.01 (3H, doublet, J = 6 Hz);
1.12 (3H, doublet, J = 6 Hz);
1.5 - 1.8 (6H, multiplet);
1.8 - 2.3 (11H, multiplet);
2.3 - 3.1 (6H, multiplet);
4.92 (1H, singlet);

6.7 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 507, 203.

Compound No. 2-6:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1740, 1640, 1500, 1460, 1220, 1150, 1050.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.7 - 4.6 (30H, multiplet);
4.19 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 495, 203.

Compound No. 2-8:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3305, 2975, 2925, 2825, 1680, 1600, 1500.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.18 (6H, doublet, J = 6 Hz);
2.12 (6H, singlet);
2.21 (3H, singlet);
2.2 - 3.4 (8H, multiplet);
5.12 (1H, singlet);
6.7 - 7.7 (10H, multiplet);
6.67 (1H, broad singlet).
Mass Spectrum (m/e): 491, 203.

Compound No. 2-9:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 2960, 2940, 2830, 1685, 1600, 1510.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.06 (3H, doublet, J = 6 Hz);
1.16 (3H, doublet, J = 6 Hz);
2.1 - 3.0 (6H, multiplet);
3.08 (1H, singlet);
3.17 (1H, singlet);
3.78 (3H, singlet);
3.81 (6H, singlet);
5.03 (1H, singlet);
6.86 (2H, singlet);
6.7 - 7.7 (8H, multiplet);
9.13 (1H, broad singlet).
Mass Spectrum (m/e): 539, 203.

Compound No. 2-10:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3280, 2950, 2800, 1700, 1625, 1600, 1530, 1500.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.05 (3H, doublet, J = 6 Hz);
1.15 (3H, doublet, J = 6 Hz);
1.7 - 2.1 (6H, multiplet);
3.08 (1H, AB-type, J = 18 Hz);
3.23 (1H, AB-type, J = 18 Hz);
4.99 (1H, singlet);
6.4 - 7.7 (9H, multiplet);
7.9 - 8.5 (2H, multiplet);

9.70 (1H, broad singlet).
Mass Spectrum (m/e): 485, 203.

Compound No. 2-12:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1670, 1600, 1500, 1440, 1220, 1140.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.08 (3H, doublet, J = 6 Hz);
1.8 - 2.3 (1H, multiplet);
2.4 - 2.7 (6H, multiplet);
2.95 (1H, doublet, J = 18 Hz);
3.45 (1H, doublet, J = 18 Hz);
4.22 (1H, singlet);
6.6 - 7.7 (12H, multiplet);
9.35 (1H, singlet).
Mass Spectrum (m/e): 453, 203.

Compound No. 2-13:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1500, 1450, 1410, 1220, 1130, 1020.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.0 (3H, doublet, J = 6 Hz);
1.76 - 3.0 (7H, multiplet);
2.9 (1H, doublet, J = 16 Hz);
3.4 (1H, doublet, J = 16 Hz);
3.77 (3H, singlet);
3.84 (6H, singlet);
4.21 (1H, singlet);
6.8 - 7.56 (10H, multiplet);
9.1 (1H, singlet).
Mass Spectrum (m/e): 525, 203.

Compound No. 2-14:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1620, 1610, 1450, 1320, 1220, 1150, 1100.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.01 (3H, doublet, J = 6 Hz);
1.73 - 2.98 (7H, multiplet);
2.93 (1H, doublet, J = 17 Hz);
3.48 (1H, doublet, J = 17 Hz);
4.22 (1H, singlet);
6.78 - 7.58 (11H, multiplet);
8.23 - 8.68 (1H, multiplet);
9.76 (1H, singlet).
Mass Spectrum (m/e): 453, 203.

Compound No. 2-15:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1600, 1500, 1400, 1300, 1220, 1050.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.98 (3H, doublet, J = 6 Hz);
1.6 - 3.2 (7H, multiplet);
2.9 (1H, doublet, J = 16 Hz);
3.45 (1H, doublet, J = 16 Hz);

4.21 (1H, singlet);
6.7 - 7.8 (12H, multiplet);
9.22 (1H, multiplet).
Mass Spectrum (m/e): 453, 203.

Compound No. 2-16:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3310, 2980, 2840, 1700, 1620, 1600, 1530.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.05 (3H, doublet, J = 6 Hz);
1.16 (3H, doublet, J = 6 Hz);
2.1 - 3.0 (6H, multiplet);
3.12 (1H, singlet);
3.19 (1H, multiplet);
4.98 (1H, multiplet);
6.7 - 7.7 (11H, multiplet);
8.1 - 8.7 (1H, multiplet);
9.60 (1H, broad singlet).
Mass Spectrum (m/e): 467, 203.

Compound No. 2-17:

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:
3425, 3250, 2990, 2840, 1695, 1605, 1540, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.04 (3H, doublet, J = 6 Hz);
1.28 (3H, doublet, J = 6 Hz);
1.7 - 3.0 (6H, multiplet);
3.05 (1H, AB-type, J = 16 Hz);
3.40 (1H, AB-type, J = 16 Hz);
5.20 (1H, singlet);
7.7 - 8.0 (14H, multiplet);
8.29 (1H, doublet of doublets, J = 2.6 Hz);
10.06 (1H, broad singlet).
Mass Spectrum (m/e): 499, 203.

Compound No. 2-21:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 2990, 2840, 1735, 1690, 1600, 1515.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.15 (3H, doublet, J = 6 Hz);
1.16 (3H, doublet, J = 6 Hz);
2.1 - 3.1 (6H, multiplet);
3.10 (1H, singlet);
3.20 (1H, singlet);
5.03 (1H, singlet);
6.5 - 7.7 (12H, multiplet);
9.31 (1H, broad singlet).
Mass Spectrum (m/e): 467, 203.

Compound No. 2-22:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3290, 2950, 2810, 1680, 1605, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.05 (3H, doublet, J = 6 Hz);

1.19 (3H, doublet, J = 6 Hz);
1.7 - 3.3 (8H, multiplet);
5.04 (1H, singlet);
6.6 - 7.8 (12H, multiplet);
9.17 (1H, broad singlet).
Mass Spectrum (m/e): 467, 203.

Compound No. 2-23:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3300, 2975, 2830, 1675, 1605, 1510.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.7 - 1.5 (9H, multiplet);
1.76 (2H, sextet, J = 7 Hz);
2.2 - 3.1 (6H, multiplet);
3.07 (1H, singlet);
3.18 (1H, singlet);
3.88 (2H, triplet, J = 7 Hz);
5.06 (1H, singlet);
6.7 - 7.8 (12H, multiplet);
9.08 (1H, broad singlet).
Mass Spectrum (m/e): 507, 203.

Compound No. 2-24:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3375, 2990, 2840, 1745, 1680, 1600, 1505.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.8 - 1.5 (9H, multiplet);
1.6 - 2.9 (6H, multiplet);
2.98 (1H, singlet);
3.12 (1H, singlet);
3.8 - 4.4 (4H, multiplet);
5.08 (1H, singlet);
6.7 - 7.9 (8H, multiplet).
Mass Spectrum (m/e): 459, 203.

Compound No. 2-62:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3275, 1730, 1660, 1600, 1500, 1380, 1220, 1140.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.21 (1.5H, doublet, J = 7 Hz);
1.32 (1.5H, doublet, J = 7 Hz);
1.55 (3H, doublet, J = 7 Hz);
2.09 (6H, singlet);
2.21 (3H, singlet);
1.7 - 3.2 (7H, multiplet);
3.38 (1H, quartet, J = 7 Hz);
4.15 (1H, singlet);
5.32 (1H, quartet, J = 7 Hz);
6.7 - 7.5 (10H, multiplet);
8.8 (1H, singlet).
Mass Spectrum (m/e): 491.

Compound No. 2-63:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1600, 1510, 1380, 1300, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.0 - 1.7 (6H, multiplet);
1.9 - 3.1 (7H, multiplet);
3.45 (1H, quartet, J = 6 Hz);
4.2 (1H, singlet);
6.7 - 7.6 (11H, multiplet);
9.1 (1H, singlet).
Mass Spectrum (m/e): 485, 203.

Compound No. 2-64:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1740, 1700, 1600, 1530, 1500, 1220, 1160, 1100.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.9 - 1.5 (6H, multiplet);
1.7 - 3.1 (7H, multiplet);
3.8 (1H, quartet, J = 7 Hz);
4.22 (1H, singlet);
6.7 - 8.3 (15H, multiplet);
10.04 (1H, singlet).
Mass Spectrum (m/e): 499, 329.

Compound No. 3-1:

Infrared Absorption Spectrum (chloroform) ν_{max} cm^{-1}:
3430, 3000, 2920, 2860, 1670, 1635, 1540.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.35 (3H, doublet, J = 7 Hz);
1.5 - 1.8 (6H, multiplet);
1.8 - 2.3 (9H, multiplet);
2.3 - 3.8 (5H, multiplet);
3.92 (2H, singlet);
4.86 (1H, singlet);
6.19 (1H, singlet);
6.7 - 7.7 (8H, multiplet).
Mass Spectrum (m/e): 507, 203.

Compound No. 3-2:

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:
3225, 2910, 1665, 1600, 1500.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
2.16 (3H, singlet);
2.23 (6H, singlet);
2.68 (2H, triplet, J = 6 Hz);
3.12 (2H, singlet);
3.53 (2H, triplet, J = 6 Hz);
4.16 (2H, singlet);
4.31 (1H, singlet);
6.7 - 7.6 (8H, multiplet);
7.00 (2H, singlet);
7.85 (1H, broad singlet).
Mass Spectrum (m/e): 477, 203.

Compound No. 3-9:

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:
3250, 2925, 2800, 1690, 1625, 1510.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.43 (3H, doublet, J = 7 Hz);
2.12 (6H, singlet);
2.23 (3H, singlet);
2.4 - 2.9 (2H, multiplet);
3.08 (1H, singlet);
3.20 (1H, singlet);
3.2 - 3.7 (2H, multiplet);
4.27 (1H, singlet);
5.33 (1H, quartet, J = 7 Hz);
6.7 - 7.6 (10H, multiplet);
7.72 (1H, broad singlet).
Mass Spectrum (m/e): 491, 203.

Compound No. 3-10:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1740, 1680, 1640, 1500, 1450, 1220, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.31 (3H, doublet, J = 7 Hz);
1.5 - 3.6 (22H, multiplet);
4.26 (1H, singlet);
5.05 (1H, quartet, J = 7 Hz);
6.00 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 507, 203.

Compound No. 3-11:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1620, 1540, 1500, 1220, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.42 (3H, doublet, J = 7 Hz);
2.3 - 3.6 (7H, multiplet);
4.07 (1H, quartet, J = 7 Hz);
5.22 (1H, singlet);
6.6 - 7.7 (12H, multiplet);
8.91 (1H, singlet).
Mass Spectrum (m/e): 467, 203.

Compound No. 7-1:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3450, 1640, 1600, 1500, 1440, 1340, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.4 - 2.1 (6H, multiplet);
2.3 - 3.0 (8H, multiplet);
3.3 (2H, singlet);
3.2 - 3.7 (6H, multiplet);
4.6 (1H, singlet);
6.7 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 413, 203.

Compound No. 7-2:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1650, 1600, 1500, 1390, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.4 - 2.2 (4H, multiplet);
2.3 - 3.1 (10H, multiplet);
3.5 (2H, singlet);
3.8 (2H, triplet, J = 7 Hz);
4.58 (1H, singlet);
6.7 - 7.7 (12H, multiplet).
Mass Spectrum (m/e): 475, 203.

Compound No. 7-3:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1740, 1640, 1500, 1410, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.6 - 4.7 (30H, multiplet);
4.6 (1H, singlet);
6.7 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 495, 203.

Compound No. 7-5:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1510, 1410, 1300, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.5 - 2.1 (2H, multiplet);
2.4 - 3.1 (8H, multiplet);
3.25 (2H, singlet);
3.76 (3H, singlet);
4.61 (1H, singlet);
6.8 - 7.7 (12H, multiplet);
9.2 (1H, singlet).
Mass Spectrum (m/e): 465, 203.

Compound No. 7-6:

Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.93 (6H, doublet, J = 6 Hz);
1.5 - 2.1 (3H, multiplet);
2.4 - 3.3 (10H, multiplet);
3.18 (2H, singlet);
4.6 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 415, 203.

Compound No. 7-7:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1500, 1450, 1420, 1340, 1220, 1140.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.45 - 2.25 (2H, multiplet);
2.45 - 3.05 (8H, multiplet);
3.25 (2H, singlet);
3.8 (3H, singlet);
3.82 (6H, singlet);

4.6 (1H, singlet);
6.8 - 7.55 (10H, multiplet);
9.21 (1H, singlet).
Mass Spectrum (m/e): 525, 203.

Compound No. 7-8:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3400, 1740, 1670, 1600, 1510, 1450, 1220, 1160.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.3 - 2.0 (2H, multiplet);
2.3 - 3.0 (8H, multiplet);
3.2 (2H, singlet);
4.41 (1H, singlet);
4.52 (2H, singlet);
6.8 - 7.5 (8H, multiplet);
7.3 (5H, singlet).
Mass Spectrum (m/e): 449, 315, 245.

Compound No. 7-10:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1670, 1600, 1500, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
0.7 - 2.1 (13H, multiplet);
2.3 - 3.0 (8H, multiplet);
3.1 (2H, singlet);
4.6 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 441, 203.

Compound No. 7-11:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1740, 1680, 1600, 1500, 1370, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.5 - 2.1 (2H, multiplet);
2.18 (6H, singlet);
2.25 (3H, singlet);
2.5 - 3.1 (8H, multiplet);
3.32 (2H, singlet);
4.58 (1H, singlet);
6.8 - 7.5 (10H, multiplet);
8.7 (1H, singlet).
Mass Spectrum (m/e): 477, 203.

Compound No. 7-12:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1680, 1600, 1500, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.73 (6H, singlet);
1.46 - 2.06 (2H, multiplet);
2.46 - 3.06 (8H, multiplet);
3.1 (2H, singlet);
4.56 (1H, singlet);
6.76 - 7.56 (13H, multiplet);
7.76 (1H, singlet).

Mass Spectrum (m/e): 477, 203.

Compound No. 7-13:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1690, 1600, 1500, 1440, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.58 - 2.28 (2H, multiplet);
2.48 - 3.18 (8H, multiplet);
3.34 (2H, singlet);
4.63 (1H, singlet);
6.58 - 7.78 (12H, multiplet);
9.53 (1H, singlet).
Mass Spectrum (m/e): 453, 203.

Compound No. 7-14:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1700, 1620, 1600, 1450, 1320, 1220, 1150, 1100.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.45 - 2.05 (2H, multiplet);
2.5 - 3.1 (8H, multiplet);
3.25 (2H singlet);
4.56 (1H, singlet);
6.76 - 7.55 (11H, multiplet);
8.25 - 8.65 (1H, multiplet);
9.7 (1H, singlet).
Mass Spectrum (m/e): 453, 250, 203.

Compound No. 7-15:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3450, 3300, 1680, 1600, 1510, 1420, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.0 (3H, triplet, J = 6 Hz);
1.4 - 2.2 (4H, multiplet);
2.4 - 3.1 (8H, multiplet);
3.22 (2H, singlet);
3.88 (2H, triplet, J = 6 Hz);
4.6 (1H, singlet);
6.79 - 7.7 (10H, multiplet);
9.18 (1H, singlet).
Mass Spectrum (m/e): 493, 203.

Compound No. 7-16:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1740, 1670, 1600, 1500, 1370, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.22 (3H, triplet, J = 7 Hz);
1.4 - 2.0 (2H, multiplet);
2.3 - 3.0 (8H, multiplet);
3.14 (2H, singlet);
4.01 (2H, doublet, J = 5 Hz);
4.16 (2H, quartet, J = 7 Hz);
4.55 (1H, singlet);
6.7 - 7.5 (8H, multiplet);
7.71 (1H, triplet, J = 5 Hz).

Mass Spectrum (m/e): 445, 203.

Compound No. 7-17:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1670, 1600, 1500, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.4 - 2.2 (17H, multiplet);
2.4 - 3.0 (8H, multiplet);
3.0 (2H, singlet);
4.6 (1H, singlet);
6.8 - 7.6 (8H, multiplet).
Mass Spectrum (m/e): 493, 290, 315.

Compound No. 7-18:

Infrared Adsorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1500, 1340, 1220, 1040.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.5 - 2.2 (2H, multiplet);
2.3 - 3.1 (8H, multiplet);
3.22 (2H, singlet);
4.6 (1H, singlet);
5.88 (2H, singlet);
6.6 - 7.6 (11H, multiplet);
9.18 (1H, singlet).
Mass Spectrum (m/e): 479, 203.

Compound No. 7-26:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1700, 1600, 1150, 1010.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.5 - 2.1 (2H, multiplet);
2.4 - 3.1 (8H, multiplet);
3.31 (2H, singlet);
4.59 (1H, singlet);
6.7 - 7.7 (11H, multiplet);
8.91 (1H, singlet).
Mass Spectrum (m/e): 471.

Compound No. 7-30:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3400, 1670, 1600, 1510, 1460, 1300, 1220.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.4 - 1.9 (2H, multiplet);
2.2 - 2.9 (8H, multiplet);
3.15 (2H, singlet);
3.75 (3H, singlet);
4.35 (1H, singlet);
4.5 (2H, doublet, J = 5 Hz);
6.75 - 7.85 (13H, multiplet).
Mass Spectrum (m/e): 479, 315, 276.

Compound No. 7-38:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
1650, 1600, 1500, 1220, 830.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.18 (3H, doublet, J = 6 Hz);
1.2 - 2.2 (4H, multiplet);
2.4 - 3.0 (10H, multiplet);
3.3 - 4.2 (3H, multiplet);
4.52 (1H, singlet);
6.7 - 7.9 (12H, multiplet).
Mass Spectrum (m/e): 489, 203.

Compound No. 7-40:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1680, 1600, 1500, 1450, 1420, 1220, 1150.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.3 (3H, doublet, J = 6 Hz);
1.4 - 2.0 (2H, multiplet);
2.3 - 3.0 (8H, multiplet);
3.4 (1H, quartet, J = 6 HZ);
3.78 (6H, singlet);
4.61 (1H, singlet);
6.8 - 7.61 (1H, multiplet);
9.48 (1H, singlet).
Mass Spectrum (m/e): 509, 203.

Compound No. 7-44:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3325, 1690, 1600, 1530, 1500, 1220, 920.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.34 (3H, doublet, J = 6 Hz);
1.5 - 2.2 (2H, multiplet);
2.5 - 3.2 (8H, multiplet);
3.55 (1H, quartet, J = 6 HZ);
4.55 (1H, singlet);
6.7 - 8.4 (15H, multiplet);
10.15 (1H, singlet).
Mass Spectrum (m/e): 543, 203.

Compound No. 7-45:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3350, 1680, 1600, 1500, 1380, 1220, 1160.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.31 (3H, triplet, J = 6 Hz);
1.4 - 2.0 (2H, multiplet);
2.4 - 3.1 (8H, multiplet);
3.41 (1H, quartet, J = 6 Hz);
4.54 (1H, singlet);
6.7 - 7.5 (10H, multiplet);
8.7 (1H, singlet).
Mass Spectrum (m/e): 491, 203.

Compound No. 7-57:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3300, 1730, 1680, 1600, 1410, 1320.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.32 (3H, doublet, J = 6 Hz);
1.5 - 2.1 (2H, multiplet);
2.5 - 3.0 (8H, multiplet);
3.52 (1H, quartet, J = 6 Hz);
4.59 (1H, singlet);
6.8 - 7.7 (10H, multiplet).
Mass Spectrum (m/e): 456, 203.

Compound No. 7-58:

Infrared Absorption Spectrum (liquid) ν_{max} cm^{-1}:
3325, 1700, 1600, 1510, 1220, 1160, 1020.
Nuclear Magnetic Resonance Spectrum (60 MHz, $CDCl_3$) δ ppm:
1.28 (3H, doublet, J = 7 Hz);
1.5 - 2.1 (2H, multiplet);
2.4 - 3.1 (8H, multiplet);
3.5 (1H, quartet, J = 7 Hz);
4.6 (1H, singlet);
6.7 - 7.6 (11H, multiplet);
9.0 (1H, singlet).
Mass Spectrum (m/e): 485, 203.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

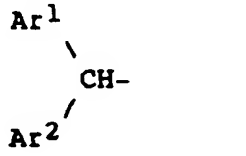
1. Compounds of formula (I):

A - M - B (I)

in which:

M represents a saturated heterocyclic group having from 5 to 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or being substituted at any of its carbon atoms by at least one C_1 - C_6 alkyl and/or oxo substituent;

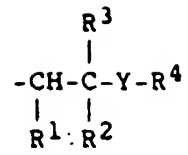
A represents a substituent on one of said nitrogen atoms and has the formula (II):



(II)

in which Ar^1 represents a phenyl group having a substituent X^1, and Ar^2 represents a phenyl group having a substituent X^2, where one of X^1 and X^2 represents a hydrogen atom or a halogen atom and the other of X^1 and X^2 represents a halogen atom;

B represents a substituent on the other nitrogen atom and has the formula (III):



(III)

in which: R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group;
R^2 and R^3 taken jointly represent an oxo group;
Y represents a group of formula $-NR^5-$;
R^4 and R^5 are the same or different and each represents a hydrogen atom, an aryl group, a C_1 – C_6 alkyl group, a substituted C_1 – C_6 alkyl group having at least one of substituents (a), a C_3 – C_{10} cycloalkyl group, an aromatic heterocyclic group or a C_2 – C_6 alkenyl group, or $-Y-R^4$ jointly represents a monocyclic heterocyclic group or a monocyclic heterocyclic group having an aromatic ring fused thereto;
said cycloalkyl groups are defined as unsubstituted or have at least one C_1 – C_4 alkyl substituent, and are saturated or have at least one ethylenically unsaturated carbon–carbon double bond;
said aryl groups are defined as carbocylic aromatic groups having from 6 to 14 ring carbon atoms and are unsubstituted or have at least one of substituents (b) and/or substituents (c);
said aromatic heterocyclic groups are defined as having a heterocyclic ring containing from 5 to 7 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero–atoms or have said heterocyclic ring fused to a heterocyclic or carbocyclic ring having from 5 to 7 ring atoms, said aromatic heterocyclic groups being unsubstituted or having at least one of substituents (b) and/or substituents (d);
said monocyclic heterocyclic groups are defined as having from 4 to 12 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero–atoms, said monocyclic heterocyclic groups being unsubstituted or having at least one of substituents (b) and/or substituents (d);
said monocyclic heterocyclic groups having an aromatic ring fused thereto are defined as having a said monocyclic heterocyclic group and a fused aromatic ring which is a heterocyclic or carbocyclic ring having from 6 to 12 ring atoms; said monocyclic heterocyclic groups and said aromatic rings being unsubstituted or having at least one of substituents (b) and/or substituents (d);
substituents (a):
halogen atoms, aryl groups, hydroxy groups, C_1 – C_6 alkoxy groups, nitro groups, cyano groups, heterocyclic groups, carboxy groups, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups, aralkyloxycarbonyl groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups and heterocyclic carboxylic acyl groups;
substituents (b):
C_1 – C_4 alkyl groups, nitro groups, cyano groups, hydroxy groups, C_1 – C_4 alkoxy groups, aryloxy groups, aralkyloxy groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyloxy groups, C_1 – C_4 alkylthio groups, arylthio groups, aralkylthio groups where the alkyl part is C_1 – C_4, C_1 – C_4 alkylsulphinyl groups, C_1 – C_4 alkylsulphonyl groups, arylsulphinyl groups, arylsulphonyl groups, C_1 – C_7 aliphatic carboxylic acylamino groups, aromatic carboxylic acylamino groups, C_2 – C_7 alkoxycarbonylamino groups, aralkyloxycarbonylamino groups where the alkyl part is C_1 – C_4, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups, aralkyloxycarbonyl groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups, heterocyclic carboxylic acyl groups, carbamoyl groups, alkylcarbamoyl groups where the alkyl part is C_1 – C_4, dialkylcarbamoyl groups where each alkyl part is C_1 – C_4, thiocarbamoyl groups, alkyl(thiocarbamoyl) groups where the alkyl part is C_1 – C_4, dialkyl(thiocarbamoyl) groups where each alkyl part is C_1 – C_4, ureido groups, alkylureido groups where the alkyl part is C_1 – C_4, dialkylureido groups where each alkyl part is C_1 – C_4, thioureido groups, alkyl(thioureido) groups where the alkyl part is C_1 – C_4, dialkyl(thioureido) groups where each alkyl part is C_1 – C_4, C_3 – C_8 cycloalkyl groups, C_5 – C_8 cycloalkenyl groups, aryl groups, heterocyclic groups, halogen atoms, C_1 – C_6 alkyl groups having at least one halogen substituent, mercapto groups, amino groups, C_1 – C_4 alkylamino groups, dialkylamino groups where each alkyl part is C_1 – C_4, carboxy groups, (C_1 – C_4 hydroxyalkyl)amino groups, di(C_1 – C_4 hydroxyalkyl)amino groups, guanidino groups and guanidino groups having at least one C_1 – C_4 alkyl substituent;
with the provisos that

any cycloalkyl groups present in the permitted substitutents are in conformity with the definition for "said cycloalkyl groups";
any aryl groups present in the permitted substitutents are in conformity with the definition for "said aryl groups";
any heterocylic groups present in the permitted substitutents are in conformity with the definition for "said aromatic heterocyclic groups", "said monocyclic heterocyclic groups", or "said monocyclic heterocylic groups having an aromatic ring fused thereto";
any substituent (a) or (b) repesenting a group which itself can be substituted with a further substituent which is a substituent (a) or (b), then that further substituent is not itself yet futher subsituted;
substituents (c):
alkylenedioxy groups having from 1 to 6 carbon atoms;
substituents (d):
oxygen atoms;
and pharmaceutically acceptable salts thereof
with the exclusion of the compound wherein M represents an unsubstituted piperazine group, A is of the formula (II) wherein Ar^1 is 4-chlorophenyl and Ar^2 is phenyl, and B is of the formula (III) wherein R^1, R^4, and R^5 are hydrogen, and R^2, R^3 and Y are as defined.

2. Compounds according to Claim 1, in which M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 - C_6 alkyl and/or oxo substituents.

3. Compounds according to Claim 1, in which M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 - C_4 alkyl and/or oxo substituents.

4. Compounds according to Claim 1, in which M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 - C_4 alkyl and/or oxo substituents.

5. Compounds according to Claim 1, in which M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 - C_4 alkyl and/or oxo substituents.

6. Compounds according to Claim 1, in which at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position.

7. Compounds according to Claim 1, in which R^1 represents a hydrogen atom or a C_1 - C_4 alkyl group.

8. Compounds according to Claim 1, in which R^1 represents a hydrogen atom or a C_1 - C_2 alkyl group.

9. Compounds according to Claim 1, in which R^1 represents a hydrogen atom or a methyl group.

10. Compounds according to any one of the preceding Claims, in which one of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and the other represents a C_6 - C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 - C_{10}, a C_6 - C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

11. Compounds according to any one of the preceding Claims, in which one of R^4 and R^5 represents a hydrogen atom, a C_1 - C_4 alkyl group or a C_2 - C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 - C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b) and/or (c).

12. Compounds according to any one of the preceding Claims, in which both of X^1 and X^2 represent fluorine atoms.

13. Compounds according to any one of Claims 1 to 12, in which one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom.

14. Compounds according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 substituents selected from C_1 – C_6 alkyl groups and oxo groups;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a C_6 – C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 – C_{10}, a C_6 – C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

15. Compounds according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a C_6 – C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 – C_{10}, a C_6 – C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

16. Compounds according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b) and/or (c).

17. Compounds according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_3 – C_4 alkyl and/or oxo substituents;
both of X^1 and X^2 represent fluorine atoms;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

18. Compounds according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

19. Compounds according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and

the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

20. Compounds according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

21. Compounds according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

22. Compounds according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
both of X^1 and X^2 represent fluorine atoms;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

23. Compounds according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

24. 1-[Bis(4-fluorophenyl)methyl]-4-(2,4,6-trimethylphenylcarbamoylmethyl)piperazine and pharmaceutically acceptable salts thereof.

25. 1-[Bis(4-fluorophenyl)methyl]-4-(1,1-dimethylbenzylcarbamoylmethyl)piperazine and pharmaceutically acceptable salts thereof.

26. 1-[Bis(4-fluorophenyl)methyl]-4-(3-fluorophenylcarbamoylmethyl)piperazine and pharmaceutically acceptable salts thereof.

27. 1-[Bis(4-fluorophenyl)methyl]-4-[N-allyl-N-(3-fluorophenyl)carbamoylmethyl]piperazine and pharmaceutically acceptable salts thereof.

28. 1-[Bis(4-fluorophenyl)methyl]-4-[1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)ethyl]piperazine and pharmaceutically acceptable salts thereof.

29. 1-[Bis(4-fluorophenyl)methyl]-4-[1-(3-fluorophenylcarbamoyl)ethyl]piperazine and pharmaceutically acceptable salts thereof.

30. 1 - (4 - Chlorobenzhydryl) - 4 - (4 - methoxyphenylcarbamoylmethyl)piperazine and pharmaceutically acceptable salts thereof.

31. 1 - (4 - Chlorobenzhydryl) - 4 - (2,4,6 - trimethylphenylcarbamoylmethyl)piperazine and pharmaceutically acceptable salts thereof.

32. 1 - [Bis(4 - fluorophenyl)methyl] - 4 - [(4 - methoxyphenyl)carbamoylmethyl] - 2,5 - dimethylpiperazine and pharmaceutically acceptable salts thereof.

33. 1 - [Bis(4 - fluorophenyl)methyl] - 4 - [(2,4,6 - trimethylphenyl)carbamoylmethyl] - 3 - methylpiperazine and pharmaceutically acceptable salts thereof.

34. 1 - [Bis(4 - fluorophenyl)methyl] - 4 - [(3 - fluorophenyl)carbamoylmethyl] - 3,3 - dimethylpiperazine and pharmaceutically acceptable salts thereof.

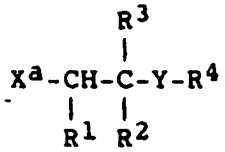
35. 1 - [Bis(4 - fluorophenyl)methyl] - 4 - [1 - (1 - adamantylcarbamoyl)ethyl]homopiperazine and pharmaceutically acceptable salts thereof.

36. A pharmaceutical composition comprising a calcium - entry blocker in admixture with a pharmaceutically acceptable carrier or diluent, in which said calcium - entry blocker is at least one compound according to any one of the preceding Claims.

37. A process for preparing a compound according to any one of Claims 1 to 35, which process comprises reacting a compound of formula (IV):

A - M - H (IV)

(in which A and M are as defined in Claim 1) or an active derivative thereof with a compound of formula (V):



(V)

(in which R^1, R^2, R^3 and R^4 are as defined in Claim 1, and X^a represents a halogen atom, a carboxylic acyloxy group or a sulphonyloxy group), and optionally, where one or both of R^4 and R^5 represents a hydrogen atom, reacting the resulting compound with an appropriate reagent to introduce an alkyl, aryl, aralkyl, aromatic heterocyclic or alkenyl group on the nitrogen atom included in the definition of $-Y-R^4$.

38. The use for the manufacture of a medicament for the treatment of vascular disorders of at least one compound according to any one of Claims 1 to 35.

39. The use for the manufacture of a medicament for the treatment of ischaemic disorders of at least one compound according to any one of Claims 1 to 35.

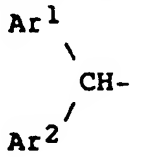
40. The use for the manufacture of a medicament of protecting an animal against the deleterious effects of anoxia of at least one compound according to any one of Claims 1 to 35.

Claims for the following Contracting States : ES, GR

1. A process for preparing a compound of formula (I):

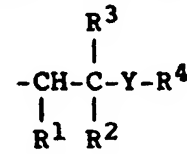
A - M - B (I)

[in which:
M represents a saturated heterocyclic group having from 5 to 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or being substituted at any of its carbon atoms by at least one C_1 – C_6 alkyl and/or oxo substituent;
A represents a substituent on one of said nitrogen atoms and has the formula (II):



(II)

in which Ar^1 represents a phenyl group having a substituent X^1, and Ar^2 represents a phenyl group having a substituent X^2, where one of X^1 and X^2 represents a hydrogen atom or a halogen atom and the other of X^1 and X^2 represents a halogen atom;
B represents a substituent on the other nitrogen atom and has the formula (III):



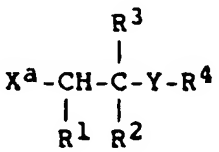
(III)

in which: R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group;
R^2 and R^3 taken jointly represent an oxo group;
Y represents a group of formula $-NR^5-$;
R^4 and R^5 are the same or different and each represents a hydrogen atom, an aryl group, a C_1 – C_6 alkyl group, a substituted C_1 – C_6 alkyl group having at least one of substituents (a), a C_3 – C_{10} cycloalkyl group, an aromatic heterocyclic group or a C_2 – C_6 alkenyl group, or $-Y-R^4$ jointly represents a monocyclic heterocyclic group or a monocyclic heterocyclic group having an aromatic ring fused thereto;
said cycloalkyl groups are defined as unsubstituted or have at least one C_1 – C_4 alkyl substituent, and are saturated or have at least one ethylenically unsaturated carbon–carbon double bond;
said aryl groups are defined as carbocyclic aromatic groups having from 6 to 14 ring carbon atoms and are unsubstituted or have at least one of substituents (b) and/or substituents (c);
said aromatic heterocyclic groups are defined as having a heterocyclic ring containing from 5 to 7 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms or have said heterocyclic ring fused to a heterocyclic or carbocyclic ring having from 5 to 7 ring atoms, said aromatic heterocyclic groups being unsubstituted or having at least one of substituents (b) and/or substituents (d);
said monocyclic heterocyclic groups are defined as having from 4 to 12 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said monocyclic heterocyclic groups being unsubstituted or having at least one of substituents (b) and/or substituents (d);
said monocyclic heterocyclic groups having an aromatic ring fused thereto are defined as having a said monocyclic heterocyclic group and a fused aromatic ring which is a heterocyclic or carbocyclic ring having from 6 to 12 ring atoms; said monocyclic heterocyclic groups and said aromatic rings being unsubstituted or having at least one of substituents (b) and/or substituents (d);
substituents (a):
halogen atoms, aryl groups, hydroxy groups, C_1 – C_6 alkoxy groups, nitro groups, cyano groups, heterocyclic groups, carboxy groups, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups, aralkyloxycarbonyl groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups and heterocyclic carboxylic acyl groups;
substituents (b):
C_1 – C_4 alkyl groups, nitro groups, cyano groups, hydroxy groups, C_1 – C_4 alkoxy groups, aryloxy groups, aralkyloxy groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyloxy groups, C_1 – C_4 alkylthio groups, arylthio groups, aralkylthio groups where the alkyl part is C_1 – C_4, C_1 – C_4 alkylsulphinyl groups, C_1 – C_4 alkylsulphonyl groups, arylsulphinyl groups, arylsulphonyl

groups, C_1 – C_7 aliphatic carboxylic acylamino groups, aromatic carboxylic acylamino groups, C_2 – C_7 alkoxycarbonylamino groups, aralkyloxycarbonylamino groups where the alkyl part is C_1 – C_4, C_2 – C_7 alkoxycarbonyl groups, aryloxycarbonyl groups, aralkyloxycarbonyl groups where the alkyl part is C_1 – C_4, C_1 – C_7 aliphatic carboxylic acyl groups, aromatic carboxylic acyl groups, heterocyclic carboxylic acyl groups, carbamoyl groups, alkylcarbamoyl groups where the alkyl part is C_1 – C_4, dialkylcarbamoyl groups where each alkyl part is C_1 – C_4, thiocarbamoyl groups, alkyl(thiocarbamoyl) groups where the alkyl part is C_1 – C_4, dialkyl(thiocarbamoyl) groups where each alkyl part is C_1 – C_4, ureido groups, alkylureido groups where the alkyl part is C_1 – C_4, dialkylureido groups where each alkyl part is C_1 – C_4, thioureido groups, alkyl(thioureido) groups where the alkyl part is C_1 – C_4, dialkyl(thioureido) groups where each alkyl part is C_1 – C_4, C_3 – C_8 cycloalkyl groups, C_5 – C_8 cycloalkenyl groups, aryl groups, heterocyclic groups, halogen atoms, C_1 – C_6 alkyl groups having at least one halogen substituent, mercapto groups, amino groups, C_1 – C_4 alkylamino groups, dialkylamino groups where each alkyl part is C_1 – C_4, carboxy groups, (C_1 – C_4 hydroxyalkyl)amino groups, di(C_1 – C_4 hydroxyalkyl)amino groups, guanidino groups and guanidino groups having at least one C_1 – C_4 alkyl substituent;
with the provisos that
any cycloalkyl groups present in the permitted substitutents are in conformity with the definition for "said cycloalkyl groups";
any aryl groups present in the permitted substitutents are in conformity with the definition for "said aryl groups";
any heterocylic groups present in the permitted substitutents are in conformity with the definition for "said aromatic heterocyclic groups", "said monocyclic heterocyclic groups", or "said monocyclic heterocylic groups having an aromatic ring fused thereto";
any substituent (a) or (b) repesenting a group which itself can be substituted with a further substituent which is a substituent (a) or (b), then that further substituent is not itself yet futher subsituted;
substituents (c):
alkylenedioxy groups having from 1 to 6 carbon atoms;
substituents (d):
oxygen atoms;
and pharmaceutically acceptable salts thereof
with the exclusion of the compound wherein M represents an unsubstituted piperazine group, A is of the formula (II) wherein Ar^1 is 4-chlorophenyl and Ar^2 is phenyl, and B is of the formula (III) wherein R^1 R^4, and R^5 are hydrogen, and R^2, R^3 and Y are as defined,
which process comprises reacting a compound of formula (IV):

A – M – H (IV)

(in which A and M are as defined above) or an active derivative thereof with a compound of formula (V):



(V)

(in which R^1, R^2, R^3 and R^4 are as defined above, and X^a represents a halogen atom, a carboxylic acyloxy group or a sulphonyloxy group), and optionally, where one or both of R^4 and R^5 represents a hydrogen atom, reacting the resulting compound with an appropriate reagent to introduce an alkyl, aryl, aralkyl, aromatic heterocyclic or alkenyl group on the nitrogen atom included in the definition of –Y–R^4.

2. A process according to Claim 1, in which M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_6 alkyl and/or oxo substituents.

3. A process according to Claim 1, in which M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents.

4. A process according to Claim 1, in which M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents.

5. A process according to Claim 1, in which M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents.

6. A process according to Claim 1, in which at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position.

7. A process according to Claim 1, in which R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group.

8. A process according to Claim 1, in which R^1 represents a hydrogen atom or a C_1 – C_2 alkyl group.

9. A process according to Claim 1, in which R^1 represents a hydrogen atom or a methyl group.

10. A process according to any one of the preceding Claims, in which one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a C_6 – C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 – C_{10}, a C_6 – C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

11. A process according to any one of the preceding Claims, in which one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b) and/or (c).

12. A process according to any one of the preceding Claims, in which both of X^1 and X^2 represent fluorine atoms.

13. A process according to any one of Claims 1 to 12, in which one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom.

14. A process according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 substituents selected from C_1 – C_6 alkyl groups and oxo groups; and
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl, group or a C_2 – C_4 alkenyl group and the other represents a C_6 – C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 – C_{10}, a C_6 – C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

15. A process according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a C_6 – C_{10} carbocyclic aryl group, an aralkyl group in which the aryl part is C_6 – C_{10}, a C_6 – C_{10} cycloalkyl group or said aryl or aralkyl group having at least one of substituents (b) and/or (c).

16. A process according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b) and/or (c).

17. A process according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_3 – C_4 alkyl and/or oxo substituents;
both of X^1 and X^2 represent fluorine atoms;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

18. A process according to Claim 1, in which:
M represents a saturated heterocyclic group having 6 or 7 ring atoms of which 2 are nitrogen atoms, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

19. A process according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_6 alkyl group;
R^2 and R^3 together represent an oxo group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

20. A process according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms from 1 to 4 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

21. A process according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
at least one of Ar^1 and Ar^2 represents a phenyl group having a halogen substituent at its 4-position;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group: and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

22. A process according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
both of X^1 and X^2 represent fluorine atoms;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

23. A process according to Claim 1, in which:
M represents a piperazinyl group or a homopiperazinyl group, said group being unsubstituted or having at any of its carbon atoms 1 or 2 C_1 – C_4 alkyl and/or oxo substituents;
one of X^1 and X^2 represents a chlorine atom and the other represents a hydrogen atom;
R^1 represents a hydrogen atom or a C_1 – C_4 alkyl group; and
one of R^4 and R^5 represents a hydrogen atom, a C_1 – C_4 alkyl group or a C_2 – C_4 alkenyl group and the other represents a phenyl group, a benzyl group, a C_6 – C_{10} cycloalkyl group or said phenyl or benzyl group having at least one of substituents (b).

24. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare:
1 – [bis(4 – fluorophenyl)methyl] – 4 – (2,4,6 – trimethylphenylcarbamoylmethyl)piperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – (1,1 – dimethylbenzylcarbamoylmethyl)piperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – (3 – fluorophenylcarbamoylmethyl)piperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [N – allyl – N – (3 – fluorophenyl)carbamoylmethyl]piperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [1 – (1,2,3,4 – tetrahydroquinoline – 1 – carbonyl)ethyl]piperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [1 – (3 – fluorophenylcarbamoyl)ethyl]piperazine;
1 – (4 – chlorobenzhydryl) – 4 – (4 – methoxyphenylcarbamoylmethyl)piperazine;
1 – (4 – chlorobenzhydryl) – 4 – (2,4,6 – trimethylphenylcarbamoylmethyl)piperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [(4 – methoxyphenyl)carbamoylmethyl] – 2,5 – dimethylpiperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [(2,4,6 – trimethylphenyl)carbamoylmethyl] – 3 – methylpiperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [(3 – fluorophenyl)carbamoylmethyl] – 3,3 – dimethylpiperazine;
1 – [bis(4 – fluorophenyl)methyl] – 4 – [1 – (1 – adamantylcarbamoyl)ethyl]homopiperazine;
or a pharmaceutically acceptable salt thereof.

25. The use for the manufacture of a medicament for the treatment of vascular disorders of at least one compound of formula (I), as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

26. The use for the manufacture of a medicament for the treatment of ischaemic disorders of at least one compound of formula (I), as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

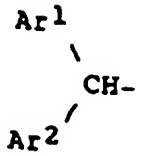
27. The use for the manufacture of a medicament of protecting an animal against the deleterious effects of anoxia of at least one compound of formula (I), as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindungen der Formel (I):

A – M – B (I)

in welcher:
M eine gesättigte heterocyclische Gruppe mit 5 bis 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe entweder unsubstituiert oder an beliebigen ihrer Kohlenstoffatome durch mindestens einen C_1 – C_6 – Alkyl – und/oder Oxosubstituenten substituiert ist,
A einen Substituenten an einem der genannten Stickstoffatome darstellt und die Formel (II) hat:

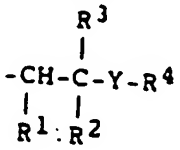


(II)

in welcher

Ar^1 eine Phenylgruppe mit einem Substituenten X^1 darstellt und Ar^2 eine Phenylgruppe mit einem Substituenten X^2 darstellt, wobei eines von X^1 und X^2 ein Wasserstoffatom oder Halogenatom darstellt, und der andere von X^1 und X^2 ein Halogenatom darstellt,

B einen Substituenten am anderen Stickstoffatom darstellt und die Formel (III) besitzt:



(III)

in welcher:

R^1 ein Wasserstoffatom oder eine C_1-C_6 - Alkylgruppe darstellt,

R^2 und R^3 gemeinsam eine Oxogruppe darstellen,

Y eine Gruppe der Formel $-NR^5-$ darstellt,

R^4 und R^5 gleich oder verschieden voneinander sind und jeweils ein Wasserstoffatom, eine Arylgruppe, eine C_1-C_6 - Alkylgruppe, eine substituierte C_1-C_6 - Alkylgruppe mit mindestens einem der Substituenten (a), eine C_3-C_{10} - Cycloalkylgruppe, eine aromatische heterocyclische Gruppe oder eine C_2-C_6 - Alkenylgruppe darstellen, oder $-Y-R^4$ gemeinsam eine monocyclische heterocyclische Gruppe oder eine monocyclische heterocyclische Gruppe mit einem ankondensierten aromatischen Ring darstellt,

wobei die Cycloalkylgruppen als solche definiert sind, die unsubstituiert sind oder mindestens einen C_1-C_4 - Alkylsubstituenten aufweisen, und

gesättigt sind oder mindestens eine ethylenisch ungesättigte Kohlenstoff - Kohlenstoff Doppelbindung aufweisen,

die Arylgruppen als carbocyclische aromatische Gruppen definiert sind, die 6 bis 14 Ringkohlenstoffatome aufweisen und entweder unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder (c) aufweisen,

die aromatischen heterocyclischen Gruppen als solche definiert sind, die einen heterocyclischen Ring aufweisen, welcher 5 bis 7 Ringatome enthält, von denen 1 bis 3 Stickstoff- und/oder Sauerstoff- und/oder Schwefel- Heteroatome sind, oder den heterocyclischen Ring an einen heterocyclischen oder carbocyclischen Ring mit 5 bis 7 Ringatomen ankondensiert aufweisen, wobei die aromatischen heterocyclischen Gruppen unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder Substituenten (d) aufweisen,

die monocyclischen heterocyclischen Gruppen definiert sind als solche mit 4 bis 12 Ringatomen, von denen 1 bis 5 Stickstoff- und/oder Sauerstoff- und/oder Schwefel- Heteroatome sind, wobei die monocyclischen heterocyclischen Gruppen unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder Substituenten (d) aufweisen,

die monocyclischen heterocyclischen Gruppen mit einem ankondensierten aromatischen Ring definiert sind als solche mit der genannten monocyclischen heterocyclischen Gruppe und einem ankondensierten aromatischen Ring, welcher ein heterocyclischer oder carbocyclischer Ring mit 6 bis 12 Ringatomen ist, wobei die monocyclischen heterocyclischen Gruppen und die aromatischen Ringe unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder Substituenten (d) aufweisen;

Substituenten (a):

Halogenatome, Arylgruppen, Hydroxylgruppen, C_1-C_6 - Alkoxygruppen, Nitrogruppen, Cyangruppen, heterocyclische Gruppen, Carboxylgruppen, C_2-C_7 - Alkoxycarbonylgruppen, Aryloxycarbonylgruppen, Aralkyloxycarbonylgruppen mit einem C_1-C_4 - Alkylteil, Acylgruppen von C_1-C_7 - aliphatischen Car-

bonsäuren, Acylgruppen von aromatischen Carbonsäuren und Acylgruppen von heterocyclischen Carbonsäuren;
Substituenten (b):
C_1-C_4-Alkylgruppen, Nitrogruppen, Cyangruppen, Hydroxylgruppen, C_1-C_4-Alkoxygruppen, Aryloxygruppen, Aralkyloxygruppen mit einem C_1-C_4-Alkylteil, C_1-C_7-Acyloxygruppen von aliphatischen Carbonsäuren, C_1-C_4-Alkylthiogruppen, Arylthiogruppen, Aralkylthiogruppen mit einem C_1-C_4-Alkylteil, C_1-C_4-Alkylsulfinylgruppen, C_1-C_4-Alkylsulfonylgruppen, Arylsulfinylgruppen, Arylsulfonylgruppen, Acylaminogruppen von C_1-C_7-aliphatischen Carbonsäuren, Acylaminogruppen aromatischer Carbonsäuren, C_2-C_7-Alkoxycarbonylaminogruppen, Aralkyloxycarbonylaminogruppen mit einem C_1-C_4-Alkylteil, C_2-C_7-Alkoxycarbonylgruppen, Aryloxycarbonylgruppen, Aralkyloxycarbonylgruppen mit einem C_1-C_4-Alkylteil, Acylgruppen von C_1-C_7-aliphatischen Carbonsäuren, Acylgruppen aromatischer Carbonsäuren, Acylgruppen von heterocyclischen Carbonsäuren, Carbamoylgruppen, Alkylcarbamoylgruppen mit einem C_1-C_4-Alkylteil, Dialkylcarbamoylgruppen mit einem Alkylteil von jeweils C_1-C_4, Thiocarbamoyl-Gruppen, Alkyl(thiocarbamoyl)-Gruppen mit einem C_1-C_4-Alkylteil, Dialkyl(thiocarbamoyl)-Gruppen mit jeweils einem C_1-C_4-Alkylteil, Ureidogruppen, Alkylureidogruppen mit einem C_1-C_4-Alkylteil, Dialkylureidogruppen mit jeweils einem C_1-C_4-Alkylteil,Thioureidogruppen, Alkyl(thioureido)-Gruppen mit einem C_1-C_4-Alkylteil, Dialkyl-(thioureido)-Gruppen mit jeweils einem C_1-C_4-Teil, C_3-C_8-Cycloalkylgruppen, C_5-C_8-Cycloalkenylgruppen, Arylgruppen, heterocyclische Gruppen, Halogenatome, C_1-C_6-Alkylgruppen mit mindestens einem Halogensubstituenten, Mercaptogruppen, Aminogruppen, C_1-C_4-Alkylaminogruppen, Dialkylaminogruppen mit jeweils einem C_1-C_4-Alkylteil, Carboxylgruppen, (C_1-C_4-Hydroxyalkyl)-aminogruppen, Di(C_1-C_4-hydroxyalkyl)aminogruppen, Guanidinogruppen und Guadininogruppen mit mindestens einem C_1-C_4-Alkylsubstituenten,
unter der Voraussetzung, daß
jede in den zugelassenen Substituenten vorhandene Cycloalkylgruppe in Übereinstimmung mit der Definition für "die genannten Cycloalkylgruppen" ist,
jede in den zugelassenen Substituenten vorhandene Arylgruppe in Übereinstimmung mit der Definition für "die genannten Arylgruppen" ist,
jede in den zugelassenen Substituenten vorhandene heterocyclische Gruppe in Übereinstimmung mit der Definition für "die genannten aromatischen heterocyclischen Gruppen", "die genannten monocyclischen heterocyclischen Gruppen" oder "die genannten monocyclischen heterocyclischen Gruppen mit einem ankondensierten aromatischen Ring" ist,
im Fall eines Substituenten (a) oder (b), der eine Gruppe darstellt, welche selbst substituiert sein kann mit einem weiteren Substituenten (a) oder (b), dieser weitere Substituent dann jedoch selbst nicht weiter substituiert ist;
Substituenten (c):
Alkylendioxygruppen mit 1 bis 6 Kohlenstoffatomen;
Substituenten (d):
Sauerstoffatome;
und pharmazeutisch verträgliche Salze derselben,
unter Ausschluß solcher Verbindungen, worin M eine unsubstituierte Piperazingruppe darstellt, A der Formel (II) entspricht, worin Ar^1 4-Chlorphenyl und Ar^2 Phenyl ist, und B der Formel (III) entspricht, worin R^1, R^4 und R^5 Wasserstoffsind, und R^2, R^3 und Y wie definiert sind.

2. Verbindungen gemäß Anspruch 1, in welchen M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannten Gruppen unsubstituiert sind oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1-C_6-Alkyl- und/oder Oxosubstituenten aufweisen.

3. Verbindungen gemäß Anspruch 1, in welchen M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannten Gruppen unsubstituiert sind oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweisen.

4. Verbindungen gemäß Anspruch 1, in welchen M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweist.

5. Verbindungen gemäß Anspruch 1, in welchen M eine Piperazinylgruppe oder eine Homopiperazinyl-gruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweist.

6. Verbindungen gemäß Anspruch 1, in welchen mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in 4-Position darstellt.

7. Verbindungen gemäß Anspruch 1, in welchen R^1 ein Wasserstoffatom oder eine C_1-C_4-Alkylgruppe darstellt.

8. Verbindungen gemäß Anspruch 1, in welchen R^1 ein Wasserstoffatom oder eine C_1-C_2-Alkylgruppe darstellt.

9. Verbindungen gemäß Anspruch 1, in welchen R^1 ein Wasserstoffatom oder eine Methylgruppe darstellt.

10. Verbindungen gemäß einem der vorhergehenden Ansprüche, in welchen eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine C_6-C_{10}-carbocyclische Arylgruppe, eine Aralkylgruppe mit einem C_6-C_{10}-Arylteil, eine C_6-C_{10}-Cycloalkylgruppe oder die genannte Aryl- oder Aralkylgruppe mit mindestens einem Substituenten (b) und/oder (c), darstellt.

11. Verbindungen gemäß einem der vorhergehenden Ansprüche, in welchen eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6-C_{10}-Cycloalkylgruppe oder die genannte Phenyl- oder Benzylgruppe mit mindestens einem Substituenten (b) und/oder (c) darstellt.

12. Verbindungen gemäß einem der vorhergehenden Ansprüche, in welchen beide Reste X^1 und X^2 Fluoratome darstellen.

13. Verbindungen gemäß einem der Ansprüche 1 bis 12, in welchen eines von X^1 und X^2 ein Chloratom darstellt und das andere ein Wasserstoffatom darstellt.

14. Verbindungen gemäß Anspruch 1, in welchen:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 Substituenten, ausgewählt unter C_1-C_6-Alkylgruppen und Oxogruppen, aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4-Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine C_6-C_{10}-carbocyclische Arylgruppe, eine Aralkylgruppe mit einem C_6-C_{10}-Arylteil, eine C_6-C_{10}-Cycloalkylgruppe oder eine der genannten Aryl- oder Aralkylgruppen mit mindestens einem der Substituenten (b) und/oder (c) darstellt.

15. Verbindungen gemäß Anspruch 1, in welchen:
M eine gesättigte heteroyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4-Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1-C_4-Alkylgruppe darstellt; und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine C_6-C_{10}-carbocyclische Arylgruppe, eine Aralkylgruppe mit einem C_6-C_{10}-Arylteil, eine C_6-C_{10}-Cycloalkylgruppe oder die genannte Aryl- oder Aralkylgruppe mit mindestens einem der Substituenten (b) und/oder (c) darstellt.

16. Verbindungen gemäß Anspruch 1, in welchen:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind,

darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt;
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgrup – pe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) und/oder (c) darstellt.

17. Verbindungen gemäß Anspruch 1, in welchen:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_3 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
beide Reste X^1 und X^2 Fluoratome darstellen,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgrup – pe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

18. Verbindungen gemäß Anspruch 1, in welchen:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
eines von X^1 und X^2 ein Chloratom darstellt und das andere ein Wasserstoffatom darstellt,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgrup – pe und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

19. Verbindungen gemäß Anspruch 1, in welchen:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1 – C_4 – Alkyl – und/oder Oxo – substituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1 – C_6 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgrup – pe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

20. Verbindungen gemäß Anspruch 1, in welchen:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1 – C_4 – Alkyl – und/oder Oxo – substituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgrup – pe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, ein C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

21. Verbindungen gemäß Anspruch 1, in welchen:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist;
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt;

R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

22. Verbindungen gemäß Anspruch 1, in welchem:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
beide Reste X^1 und X^2 Fluoratome darstellen,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

23. Verbindungen gemäß Anspruch 1, in welchen:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist;
eines von X^1 und X^2 ein Chloratom darstellt und das andere ein Wasserstoffatom darstellt;
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

24. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – (2,4,6 – trimethylphenylcarbamoylmethyl)piperazin und pharmazeutisch verträgliche Salze desselben.

25. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – (1,1 – dimethylbenzylcarbamoylmethyl)piperazin und pharmazeutisch verträgliche Salze desselben.

26. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – (3 – fluorphenylcarbamoylmethyl)piperazin und pharmazeutisch verträgliche Salze desselben.

27. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [N – allyl – N – (3 – fluorphenyl)carbamoylmethyl]piperazin und pharmazeutisch verträgliche Salze desselben.

28. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [1 – (1,2,3,4 – tetrahydroquinolin – 1 – carbonyl)ethyl]piperazin und pharmazeutisch verträgliche Salze desselben.

29. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [1 – (3 – fluorphenylcarbamoyl)ethyl]piperazin und pharmazeutisch verträgliche Salze desselben.

30. 1 – (4 – Chlorbenzhydryl) – 4 – (4 – methoxyphenylcarbamoylmethyl)piperazin und pharmazeutisch verträgliche Salze desselben.

31. 1 – (4 – Chlorbenzhydryl) – 4 – (2,4,6 – trimethylphenylcarbamoylmethyl)piperazin und pharmazeutisch verträgliche Salze desselben.

32. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [(4 – methoxyphenyl)carbamoylmethyl] – 2,5 – dimethylpiperazin und pharmazeutisch verträgliche Salze desselben.

33. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [(2,4,6 – trimethylphenyl)carbamoylmethyl] – 3 – methylpiperazin und pharmazeutisch verträgliche Salze desselben.

34. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [(3 – fluorphenyl)carbamoylmethyl] – 3,3 – dimethylpiperazin und pharmazeutisch verträgliche Salze desselben.

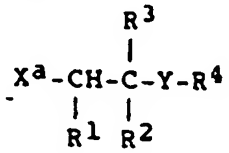
35. 1 – [Bis(4 – fluorphenyl)methyl] – 4 – [1 – (1 – adamantylcarbamoyl)ethyl]homopiperazin und pharmazeutisch verträgliche Salze desselben.

36. Arzneimittelzusammensetzung, welche eine den Calciumeintritt blockierende Verbindung zusammen mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel enthält, in welcher die genannte, den Calciumeintritt blockierende Verbindung mindestens eine Verbindung gemäß einem der vorhergehenden Ansprüche ist.

37. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1 bis 35, welches folgende Schritte umfaßt: Umsetzen einer Verbindung der Formel (IV):

A – M – H (IV)

(in welcher A und M wie in Anspruch 1 definiert sind), oder eines aktiven Derivats desselben mit einer Verbindung der Formel (V):



(V)

(in welcher R^1, R^2, R^3 und R^4 wie in Anspruch 1 definiert sind und X^a ein Halogenatom, eine Acyloxygruppe einer Carbonsäure oder eine Sulfonyloxygruppe darstellt), und, wahlweise, wenn eines oder beide von R^4 und R^5 ein Wasserstoffatom darstellt,
Umsetzen der resultierenden Verbindung mit einem geeigneten Reagenz um eine Alkyl –, Aryl –, Aralkyl –, aromatische heterocyclische oder Alkenylgruppe an dem in der Definition von –Y–R^4 enthaltenen Stickstoffatom einzuführen.

38. Verwendung mindestens einer Verbindung gemäß einem der Ansprüche 1 bis 35 zur Herstellung eines Arzneimittels zur Behandlung von Gefäßkrankheiten.

39. Verwendung mindestens einer Verbindung gemäß einem der Ansprüche 1 bis 35 zur Herstellung eines Arzneimittels zur Behandlung von ischaemischen Krankheiten.

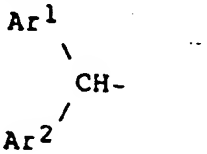
40. Verwendung mindestens einer Verbindung gemäß einem der Ansprüche 1 bis 35 zur Herstellung eines Arzneimittels zum Schutz eines Lebewesens gegen die nachteiligen Auswirkungen der Anoxie.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel (I):

A – M – B (I)

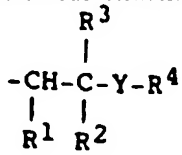
in welcher:
M eine gesättigte heterocyclische Gruppe mit 5 bis 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe entweder unsubstituiert oder an beliebigen ihrer Kohlenstoffatome durch mindestens einen $C_1 – C_6$ – Alkyl – und/oder Oxosubstituenten substituiert ist,
A einen Substituenten an einem der genannten Stickstoffatome darstellt und die Formel (II) hat:



(II)

in welcher

Ar^1 eine Phenylgruppe mit einem Substituenten X^1 darstellt und Ar^2 eine Phenylgruppe mit einem Substituenten X^2 darstellt, wobei eines von X^1 und X^2 ein Wasserstoffatom oder Halogenatom darstellt, und der andere von X^1 und X^2 ein Halogenatom darstellt,
B einen Substituenten am anderen Stickstoffatom darstellt und die Formel (III) besitzt:



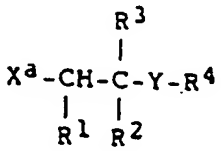
(III)

in welcher:
R^1 ein Wasserstoffatom oder eine $C_1 - C_6$ - Alkylgruppe darstellt,
R^2 und R^3 gemeinsam eine Oxogruppe darstellen,
Y eine Gruppe der Formel $-NR^5-$ darstellt,
R^4 und R^5 gleich oder verschieden voneinander sind und jeweils ein Wasserstoffatom, eine Arylgruppe, eine $C_1 - C_6$ - Alkylgruppe, eine substituierte $C_1 - C_6$ - Alkylgruppe mit mindestens einem der Substituenten (a), eine $C_3 - C_{10}$ - Cycloalkylgruppe, eine aromatische heterocyclische Gruppe oder eine $C_2 - C_6$ - Alkenylgruppe darstellen, oder $-Y-R^4$ gemeinsam eine monocyclische heterocyclische Gruppe oder eine monocyclische heterocyclische Gruppe mit einem ankondensierten aromatischen Ring darstellt,
wobei die Cycloalkylgruppen als solche definiert sind, die unsubstituiert sind oder mindestens einen $C_1 - C_4$ - Alkylsubstituenten aufweisen, und
gesättigt sind oder mindestens eine ethylenisch ungesättigte Kohlenstoff - Kohlenstoff Doppelbindung aufweisen,
die Arylgruppen als carbocyclische aromatische Gruppen definiert sind, die 6 bis 14 Ringkohlenstoffatome aufweisen und entweder unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder (c) aufweisen,
die aromatischen heterocyclischen Gruppen als solche definiert sind, die einen heterocyclischen Ring aufweisen, welcher 5 bis 7 Ringatome enthält, von denen 1 bis 3 Stickstoff- und/oder Sauerstoff- und/oder Schwefel- Heteroatome sind, oder den heterocyclischen Ring an einen heterocyclischen oder carbocyclischen Ring mit 5 bis 7 Ringatomen ankondensiert aufweisen, wobei die aromatischen heterocyclischen Gruppen unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder Substituenten (d) aufweisen,
die monocyclischen heterocyclischen Gruppen definiert sind als solche mit 4 bis 12 Ringatomen, von denen 1 bis 5 Stickstoff- und/oder Sauerstoff- und/oder Schwefel- Heteroatome sind, wobei die monocyclischen heterocyclischen Gruppen unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder Substituenten (d) aufweisen,
die monocyclischen heterocyclischen Gruppen mit einem ankondensierten aromatischen Ring definiert sind als solche mit der genannten monocyclischen heterocyclischen Gruppe und einem ankondensierten aromatischen Ring, welcher ein heterocyclischer oder carbocyclischer Ring mit 6 bis 12 Ringatomen ist, wobei die monocyclischen heterocyclischen Gruppen und die aromatischen Ringe unsubstituiert sind oder mindestens einen der Substituenten (b) und/oder Substituenten (d) aufweisen;
Substituenten (a):
Halogenatome, Arylgruppen, Hydroxylgruppen, $C_1 - C_6$ - Alkoxygruppen, Nitrogruppen, Cyangruppen, heterocyclische Gruppen, Carboxylgruppen, $C_2 - C_7$ - Alkoxycarbonylgruppen, Aryloxycarbonylgruppen, Aralkyloxycarbonylgruppen mit einem $C_1 - C_4$ - Alkylteil, Acylgruppen von $C_1 - C_7$ - aliphatischen Carbonsäuren, Acylgruppen von aromatischen Carbonsäuren und Acylgruppen von heterocyclischen Carbonsäuren;
Substituenten (b):
$C_1 - C_4$ - Alkylgruppen, Nitrogruppen, Cyangruppen, Hydroxylgruppen, $C_1 - C_4$ - Alkoxygruppen, Aryloxygruppen, Aralkyloxygruppen mit einem $C_1 - C_4$ - Alkylteil, $C_1 - C_7$ - Acyloxygruppen von aliphatischen Carbonsäuren, $C_1 - C_4$ - Alkylthiogruppen, Arylthiogruppen, Aralkylthiogruppen mit einem $C_1 - C_4$ - Alkylteil, $C_1 - C_4$ - Alkylsulfinylgruppen, $C_1 - C_4$ - Alkylsulfonylgruppen, Arylsulfinylgruppen, Arylsulfonylgruppen, Acylaminogruppen von $C_1 - C_7$ - aliphatischen Carbonsäuren, Acylaminogruppen aromatischer Carbonsäuren, $C_2 - C_7$ - Alkoxycarbonylaminogruppen, Aralkyloxycarbonylaminogruppen mit einem $C_1 - C_4$ - Alkylteil, $C_2 - C_7$ - Alkoxycarbonylgruppen, Aryloxycarbonylgruppen, Aralkylox-

ycarbonylgruppen mit einem C_1-C_4-Alkylteil, Acylgruppen von C_1-C_7-aliphatischen Carbonsäuren, Acylgruppen aromatischer Carbonsäuren, Acylgruppen von heterocyclischen Carbonsäuren, Carbamoylgruppen, Alkylcarbamoylgruppen mit einem C_1-C_4-Alkylteil, Dialkylcarbamoylgruppen mit einem Alkylteil von jeweils C_1-C_4, Thiocarbamoyl-Gruppen, Alkyl(thiocarbamoyl)-Gruppen mit einem C_1-C_4-Alkylteil, Dialkyl(thiocarbamoyl)-Gruppen mit jeweils einem C_1-C_4-Alkylteil, Ureidogruppen, Alkylureidogruppen mit einem C_1-C_4-Alkylteil, Dialkylureidogruppen mit jeweils einem C_1-C_4-Alkylteil,Thioureidogruppen, Alkyl(thioureido)-Gruppen mit einem C_1-C_4-Alkylteil, Dialkyl-(thioureido)-Gruppen mit jeweils einem C_1-C_4-Teil, C_3-C_8-Cycloalkylgruppen, C_5-C_8-Cycloalkenylgruppen, Arylgruppen, heterocyclische Gruppen, Halogenatome, C_1-C_6-Alkylgruppen mit mindestens einem Halogensubstituenten, Mercaptogruppen, Aminogruppen, C_1-C_4-Alkylaminogruppen, Dialkylaminogruppen mit jeweils einem C_1-C_4-Alkylteil, Carboxylgruppen, (C_1-C_4-Hydroxyalkyl)-aminogruppen, Di(C_1-C_4-hydroxyalkyl)aminogruppen, Guanidinogruppen und Guadininogruppen mit mindestens einem C_1-C_4-Alkylsubstituenten,
unter der Voraussetzung, daß
jede in den zugelassenen Substituenten vorhandene Cycloalkylgruppe in Übereinstimmung mit der Definition für "die genannten Cycloalkylgruppen" ist,
jede in den zugelassenen Substituenten vorhandene Arylgruppe in Übereinstimmung mit der Definition für "die genannten Arylgruppen" ist,
jede in den zugelassenen Substituenten vorhandene heterocyclische Gruppe in Übereinstimmung mit der Definition für "die genannten aromatischen heterocyclischen Gruppen", "die genannten monocyclischen heterocyclischen Gruppen" oder "die genannten monocyclischen heterocyclischen Gruppen mit einem ankondensierten aromatischen Ring" ist,
im Fall eines Substituenten (a) oder (b), der eine Gruppe darstellt, welche selbst substituiert sein kann mit einem weiteren Substituenten (a) oder (b), dieser weitere Substituent dann jedoch selbst nicht weiter substituiert ist;
Substituenten (c):
Alkylendioxygruppen mit 1 bis 6 Kohlenstoffatomen;
Substituenten (d):
Sauerstoffatome;
und pharmazeutisch verträglicher Salze derselben,
unter Ausschluß einer Verbindung, worin M eine unsubstituierte Piperazingruppe darstellt, A der Formel (II) entspricht, worin Ar^1 4-Chlorphenyl und Ar^2 Phenyl ist, und B der Formel (III) entspricht, worin R^1, R^4 und R^5 Wasserstoffsind, und R^2, R^3 und Y wie definiert sind,
wobei das Verfahren umfaßt:
Umsetzen einer Verbindung der Formel (IV):

A - M - H (IV)

(in welcher A und M wie in Anspruch 1 definiert sind), oder eines aktiven Derivats desselben mit einer Verbindung der Formel (V):



(V)

(in welcher R^1, R^2, R^3 und R^4 wie in Anspruch 1 definiert sind und X^a ein Halogenatom, eine Acyloxygruppe einer Carbonsäure oder eine Sulfonyloxygruppe darstellt), und, wahlweise, wenn eines oder beide von R^4 und R^5 ein Wasserstoffatom darstellt,
Umsetzen der resultierenden Verbindung mit einem geeigneten Reagenz um eine Alkyl-, Aryl-, Aralkyl-, aromatische heterocyclische oder Alkenylgruppe an dem in der Definition von $-Y-R^4$ enthaltenen Stickstoffatom einzuführen.

2. Verfahren gemäß Anspruch 1, in welchem M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannten Gruppen unsubstituiert sind oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1-C_6-Alkyl- und/oder Oxosubstituenten

aufweisen.

3. Verfahren gemäß Anspruch 1, in welchem M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannten Gruppen unsubstituiert sind oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweisen.

4. Verfahren gemäß Anspruch 1, in welchem M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweist.

5. Verfahren gemäß Anspruch 1, in welchem M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1-C_4-Alkyl- und/oder Oxosubstituenten aufweist.

6. Verfahren gemäß Anspruch 1, in welchem mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in 4-Position darstellt.

7. Verfahren gemäß Anspruch 1, in welchem R^1 ein Wasserstoffatom oder eine C_1-C_4-Alkylgruppe darstellt.

8. Verfahren gemäß Anspruch 1, in welchem R^1 ein Wasserstoffatom oder eine C_1-C_2-Alkylgruppe darstellt.

9. Verfahren gemäß Anspruch 1, in welchem R^1 ein Wasserstoffatom oder eine Methylgruppe darstellt.

10. Verfahren gemäß einem der vorhergehenden Ansprüche, in welchem eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine C_6-C_{10}-carbocyclische Arylgruppe, eine Aralkylgruppe mit einem C_6-C_{10}-Arylteil, eine C_6-C_{10}-Cycloalkylgruppe oder die genannte Aryl- oder Aralkylgruppe mit mindestens einem Substituenten (b) und/oder (c), darstellt.

11. Verfahren gemäß einem der vorhergehenden Ansprüche, in welchem eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6-C_{10}-Cycloalkylgruppe oder die genannte Phenyl- oder Benzylgruppe mit mindestens einem Substituenten (b) und/oder (c) darstellt.

12. Verfahren gemäß einem der vorhergehenden Ansprüche, in welchem beide Reste X^1 und X^2 Fluoratome darstellen.

13. Verfahren gemäß einem der Ansprüche 1 bis 12, in welchem eines von X^1 und X^2 ein Chloratom darstellt und das andere ein Wasserstoffatom darstellt.

14. Verfahren gemäß Anspruch 1, in welchem:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 Substituenten, ausgewählt unter C_1-C_6-Alkylgruppen und Oxogruppen, aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4-Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine C_2-C_4-Alkenylgruppe darstellt und das andere eine C_6-C_{10}-carbocyclische Arylgruppe, eine Aralkylgruppe mit einem C_6-C_{10}-Arylteil, eine C_6-C_{10}-Cycloalkylgruppe oder eine der genannten Aryl- oder Aralkylgruppen mit mindestens einem der Substituenten (b) und/oder (c) darstellt.

15. Verfahren gemäß Anspruch 1, in welchem:
M eine gesättigte heteroyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis

4 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt; und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine C_6 – C_{10} – carbocyclische Arylgruppe, eine Aralkylgruppe mit einem C_6 – C_{10} – Arylteil, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Aryl – oder Aralkylgruppe mit mindestens einem der Substituenten (b) und/oder (c) darstellt.

16. Verfahren gemäß Anspruch 1, in welchem:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt;
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) und/oder (c) darstellt.

17. Verfahren gemäß Anspruch 1, in welchem:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_3 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
beide Reste X^1 und X^2 Fluoratome darstellen,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

18. Verfahren gemäß Anspruch 1, in welchem:
M eine gesättigte heterocyclische Gruppe mit 6 oder 7 Ringatomen, von denen 2 Stickstoffatome sind, darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
eines von X^1 und X^2 ein Chloratom darstellt und das andere ein Wasserstoffatom darstellt,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

19. Verfahren gemäß Anspruch 1, in welchem:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1 – C_4 – Alkyl – und/oder Oxo – substituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt,
R^1 ein Wasserstoffatom oder eine C_1 – C_6 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

20. Verfahren gemäß Anspruch 1, in welchem:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 bis 4 C_1 – C_4 – Alkyl – und/oder Oxo – substituenten aufweist,
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt,

R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, ein C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

21. Verfahren gemäß Anspruch 1, in welchem:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist;
mindestens eines von Ar^1 und Ar^2 eine Phenylgruppe mit einem Halogensubstituenten in der 4 – Position darstellt;
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

22. Verfahren gemäß Anspruch 1, in welchem:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist,
beide Reste X^1 und X^2 Fluoratome darstellen,
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

23. Verfahren gemäß Anspruch 1, in welchem:
M eine Piperazinylgruppe oder eine Homopiperazinylgruppe darstellt, wobei die genannte Gruppe unsubstituiert ist oder an beliebigen ihrer Kohlenstoffatome 1 oder 2 C_1 – C_4 – Alkyl – und/oder Oxosubstituenten aufweist;
eines von X^1 und X^2 ein Chloratom darstellt und das andere ein Wasserstoffatom darstellt;
R^1 ein Wasserstoffatom oder eine C_1 – C_4 – Alkylgruppe darstellt, und
eines von R^4 und R^5 ein Wasserstoffatom, eine C_1 – C_4 – Alkylgruppe oder eine C_2 – C_4 – Alkenylgruppe darstellt und das andere eine Phenylgruppe, eine Benzylgruppe, eine C_6 – C_{10} – Cycloalkylgruppe oder die genannte Phenyl – oder Benzylgruppe mit mindestens einem der Substituenten (b) darstellt.

24. Verfahren gemäß Anspruch 1, in welchem die Reagenzien und Reaktionsbedingungen so gewählt sind, daß
1 – [Bis(4 – fluorphenyl)methyl] – 4 – (2,4,6 – trimethylphenylcarbamoylmethyl)piperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – (1,1 – dimethylbenzylcarbamoylmethyl)piperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – (3 – fluorphenylcarbamoylmethyl)piperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [N – allyl – N – (3 – fluorphenyl)carbamoylmethyl]piperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [$\overline{1}$ – (1,2,3,$\overline{4}$ – tetrahydroquinolin – 1 – carbonyl)ethyl]piperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [1 – (3 – fluorphenylcarbamoyl)ethyl]piperazin,
1 – (4 – Chlorbenzhydryl) – 4 – (4 – methoxyphenylcarbamoylmethyl)piperazin,
1 – (4 – Chlorbenzhydryl) – 4 – (2,4,6 – trimethylphenylcarbamoylmethyl)piperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [(4 – methoxyphenyl)carbamoylmethyl] – 2,5 – dimethylpiperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [(2,4,6 – trimethylphenyl)carbamoylmethyl] – 3 – methylpiperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [(3 – fluorphenyl)carbamoylmethyl] – 3,3 – dimethylpiperazin,
1 – [Bis(4 – fluorphenyl)methyl] – 4 – [1 – (1 – adamantylcarbamoyl)ethyl]homopiperazin,
oder ein pharmazeutisch verträgliches Salz derselben
hergestellt wird.

25. Verwendung mindestens einer in Anspruch 1 definierten Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes derselben zur Herstellung eines Arzneimittels zur Behandlung von Gefäßkrankheiten.

26. Verwendung mindestens einer in Anspruch 1 definierten Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes derselben zur Herstellung eines Arzneimittels zur Behandlung von ischaemischen Krankheiten.

27. Verwendung mindestens einer in Anspruch 1 definierten Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes derselben zur Herstellung eines Arzneimittels zum Schutz eines Lebewesens gegen die nachteiligen Auswirkungen der Anoxie.

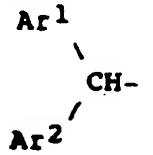
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composés de formule (I) :

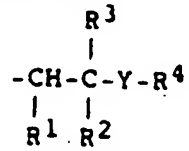
A-M-B (I)

dans laquelle :
M représente un groupe hétérocyclique saturé ayant de 5 à 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou étant substitué sur des atomes de carbone quelconques avec au moins un substituant alkyle en C_1-C_6 et/ou oxo ;
A représente un substituant sur l'un desdits atomes d'azote et a pour formule (II) :



(II)

dans laquelle Ar^1 représente un groupe phényle ayant un substituant X^1 et Ar^2 représente un groupe phényle ayant un substituant X^2, où un de X^1 et de X^2 représente un atome d'hydrogène ou un atome d'halogène et l'autre de X^1 et de X^2 représente un atome d'halogène ;
B représente un substituant sur l'autre atome d'azote et a pour formule (III) :



(III)

dans laquelle R^1 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ;
R^2 et R^3 représentent ensemble un groupe oxo ;
Y représente un groupe de formule $-NR^5-$;
R^4 et R^5 sont semblables ou différents et représentent chacun un atome d'hydrogène, un groupe aryle, un groupe alkyle en C_1-C_6, un groupe alkyle en C_1-C_6 substitué ayant au moins un des substituants (a), un groupe cycloalkyle en C_3-C_{10}, un groupe hétérocyclique aromatique ou un groupe alcénylé en C_2-C_6, ou $-Y-R^4$ conjointement représente un groupe hétérocyclique monocyclique ou un groupe hétérocyclique monocyclique auquel un cycle aromatique est condensé ;
lesdits groupes cycloalkyle sont définis comme étant non substitués ou ont au moins un substituant alkyle en C_1-C_4 et sont saturés ou ont au moins une double liaison carbone-carbone à insaturation éthylénique ;
lesdits groupes aryle sont définis comme des groupes aromatiques carbocycliques ayant de 6 à 14 atomes de carbone formant le cycle et sont non substitués ou ont au moins un des substituants (b) et/ou des substituants (c) ;
lesdits groupes hétérocycliques aromatiques sont définis comme ayant un cycle hétérocylique contenant 5 à 7 atomes formant le cycle dont 1 à 3 sont des hétéroatomes d'azote et/ou d'oxygène et/ou de soufre ou ont ledit cycle hétérocylique condensé à un cycle hétérocyclique ou carbocyclique ayant de 5 à 7 atomes formant le cycle, lesdits groupes hétérocycliques aromatiques étant non substitués ou ayant au moins un des substituants (b) et/ou des substituants (d) ;
lesdits groupes hétérocycliques monocycliques sont définis comme ayant 4 à 12 atomes formant le

cycle dont 1 à 5 sont des hétéroatomes d'azote et/ou d'oxygène et/ou de soufre, lesdits groupes hétérocycliques monocycliques étant non substitués ou ayant au moins un des substituants (b) et/ou des substituants (d) ;
lesdits groupes hétérocycliques monocycliques ayant un cycle aromatique qui leur est condensé sont définis comme ayant undit groupe hétérocyclique monocyclique et un cycle aromatique condensé qui est un cycle hétérocyclique ou carbocyclique ayant de 6 à 12 atomes formant le cycle ; lesdits groupes hétérocycliques monocycliques et lesdits cycles aromatiques étant non substitués ou ayant au moins un des substituants (b) et/ou des substituants (d) ;
substituants (a) :
atomes d'halogène, groupes aryle, groupes hydroxy, groupes alcoxy en C_1-C_6, groupes nitro, groupes cyano, groupes hétérocycliques, groupes carboxy, groupes alcoxycarbonyle en C_2-C_7, groupes aryloxycarbonyle, groupes aralkyloxycarbonyle dont la partie alkyle est en C_1-C_4, groupes acyle carboxyliques aliphatiques en C_1-C_7, groupes acyle carboxyliques aromatiques et groupes acyle carboxyliques hétérocycliques ;
substituants (b) :
groupes alkyle en C_1-C_4, groupes nitro, groupes cyano, groupes hydroxy, groupes alcoxy en C_1-C_4, groupes aryloxy, groupes aralkyloxy dont la partie alkyle est en C_1-C_4, groupes acyloxy carboxyliques aliphatiques en C_1-C_7, groupes alkylthio en C_1-C_4, groupes arylthio, groupes aralkylthio dont la partie alkyle est en C_1-C_4, groupes alkylsulfinyle en C_1-C_4, groupes alkylsulfonyle en C_1-C_4, groupes arylsulfinyle, groupes arylsulfonyle, groupes acylamino carboxyliques aliphatiques en C_1-C_7, groupes acylamino carboxyliques aromatiques, groupes alcoxycarbonylamino en C_2-C_7, groupes aralkyloxycarbonylamino dont la partie alkyle est en C_1-C_4, groupes alcoxycarbonyle en C_2-C_7, groupes aryloxycarbonyle, groupes aralkyloxycarbonyle dont la partie alkyle est en C_1-C_4, groupes acyle carboxyliques aliphatiques en C_1-C_7, groupes acyle carboxyliques aromatiques, groupes acyle carboxyliques hétérocycliques, groupes carbamoyle, groupes alkylcarbamoyle dont la partie alkyle est en C_1-C_4, groupes dialkylcarbamoyle dont chaque partie alkyle est en C_1-C_4, groupes thiocarbamoyle, groupes alkyl(thiocarbamoyle) dont la partie alkyle est en C_1-C_4, groupes dialkyl-(thiocarbamoyle) dont chaque partie alkyle est en C_1-C_4, groupes uréido, groupes alkyluréido dont la partie alkyle est en C_1-C_4, groupes dialkyluréido dont chaque partie alkyle est en C_1-C_4, groupes thio-uréido, groupes alkyl(thio-uréido) dont la partie alkyle est en C_1-C_4, groupes dialkyl(thio-uréido) dont chaque partie alkyle est en C_1-C_4, groupes cycloakyle en C_3-C_8, groupes cycloalcényle en C_5-C_8, groupes aryle, groupes hétérocycliques, atomes d' halogène, groupes alkyle en C_1-C_6 ayant au moins un substituant halogène, groupes mercapto, groupes amino, groupes alkylamino en C_1-C_4, groupes dialkylamino dont chaque partie alkyle est en C_1-C_4, groupes carboxy, groupes (hydroxyalkyl en C_1-C_4)amino, groupes di(hydroxyalkyl en C_1-C_4)amino, groupes guanidino et groupes guanidino ayant au moins un substituant alkyle en C_1-C_4 ;
avec pour réserves que
tout groupe cycloalkyle présent dans les substituants possibles est conforme à la définition de : "lesdits groupes cycloalkyle" ;
tout groupe aryle présent dans les substituants possibles est conforme à la définition de : "lesdits groupes aryle" ;
tout groupe hétérocyclique présent dans les substituants possibles est conforme aux définitions de : "lesdits groupes hétérocycliques aromatiques", "lesdits groupes hétérocycliques monocycliques" ou "lesdits groupes hétérocycliques monocycliques ayant un cycle aromatique qui leur est condensé" ;
lorsqu'un substituant (a) ou (b) représente un groupe qui lui-même peut être substitué par un autre substituant qui est un substituant (a) ou (b), alors cet autre substituant n'est pas lui-même substitué ;
substituants (c) :
groupes alkylènedioxy ayant de 1 à 6 atomes de carbone ;
substituants (d) :
atomes d'oxygène ;
et leurs sels pharmaceutiquement acceptables
à l'exclusion des composés dans lesquels M représente un groupe pipérazine non substitué, A répond à la formule (II) dans laquelle Ar^1 est un groupe 4-chlorophényle et Ar^2 est un groupe phényle et B répond à la formule (III) dans laquelle R^1, R^4 et R^5 sont un atome d'hydrogène et R^2, R^3 et Y sont comme définis.

2. Composés selon la revendication 1, où M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur

des atomes de carbone quelconques, de 1 à 4 substituants alkyle en $C_1 - C_6$ et/ou oxo.

3. Composés selon la revendication 1, où M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo.

4. Composés selon la revendication 1, où M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;

5. Composés selon la revendication 1, où M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;

6. Composés selon la revendication 1, où au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène dans sa position 4.

7. Composés selon la revendication 1, où R^1 représente un atome d' hydrogène ou un groupe alkyle en $C_1 - C_4$.

8. Composés selon la revendication 1, où R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_2$.

9. Composés selon la revendication 1, où R^1 représente un atome d'hydrogène ou un groupe méthyle.

10. Composés selon l'une quelconque des revendications précédentes, où un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe aryle carbocyclique en $C_6 - C_{10}$, un groupe aralkyle dont la partie aryle est en $C_6 - C_{10}$, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe aryle ou aralkyle ayant au moins un des substituants (b) et/ou (c).

11. Composés selon l'une quelconque des revendications précédentes, où un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b) et/ou (c).

12. Composés selon l'une quelconque des revendications précédentes, où X^1 et X^2 représentent tous deux des atomes de fluor.

13. Composés selon l'une quelconque des revendications 1 à 12, où un de X^1 et de X^2 représente un atome de chlore et l'autre représente un atome d'hydrogène.

14. Composés selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont deux sont des atomes d'azote, ledit groupe étant non substitué ou ayant sur des atomes de carbone quelconques de 1 à 4 substituants choisis parmi les groupes alkyle en $C_1 - C_6$ et les groupes oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_6$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe aryle carbocyclique en $C_6 - C_{10}$, un groupe aralkyle dont la partie aryle est en $C_6 - C_{10}$, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe aryle ou aralkyle ayant au moins un des substituants (b) et/ou (c).

15. Composés selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont deux sont des atomes d'azote, ledit groupe étant non substitué ou ayant sur un de ses atomes de carbone de 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;

au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe aryle carbocylique en $C_6 - C_{10}$, un groupe aralkyle dont la partie aryle est en $C_6 - C_{10}$, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe aryle ou aralkyle ayant au moins un des substituants (b) et/ou (c).

16. Composés selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b) et/ou (c).

17. Composés selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, un ou deux substituants alkyle en $C_3 - C_4$ et/ou oxo ;
X^1 et X^2 représentent tous deux des atomes de fluor ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

18. Composés selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
un de X^1 et de X^2 représente un atome de chlore et l'autre représente un atome d'hydrogène ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

19. Composés selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_6$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

20. Composés selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

21. Composés selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

22. Composés selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
X^1 et X^2 représentent tous deux des atomes de fluor ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

23. Composés selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
un de X^1 et de X^2 représente un atome de chlore et l'autre représente un atome d'hydrogène ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

24. 1 - [bis(4 - fluorophényl)méthyl] - 4 - (2,4,6 - triméthylphénylcarbamoylméthyl)pipérazine et ses sels pharmaceutiquement acceptables.

25. 1 - [bis(4 - fluorophényl)méthyl] - 4 - (1,1 - diméthylbenzylcarbamoylméthyl)pipérazine et ses sels pharmaceutiquement acceptables.

26. 1 - [bis(4 - fluorophényl)méthyl] - 4 - (3 - fluorophénylcarbamoylméthyl)pipérazine et ses sels pharmaceutiquement acceptables.

27. 1 - [bis(4 - fluorophényl)méthyl] - 4 - [N - allyl - N - (3 - fluorophényl)carbamoylméthyl]pipérazine et ses sels pharmaceutiquement acceptables.

28. 1 - [bis(4 - fluorophényl)méthyl] - 4 - [1 - (1,2,3,4 - tétrahydroquinoléine - 1 - carbonyl)éthyl]pipérazine et ses sels pharmaceutiquement acceptables.

29. 1 - [bis(4 - fluorophényl)méthyl) - 4 - [1 - (3 - fluorophénylcarbamoyl)éthyl]pipérazine et ses sels pharmaceutiquement acceptables.

30. 1 - (4 - chlorobenzhydryl) - 4 - (4 - méthoxyphénylcarbamoylméthyl)pipérazine et ses sels pharmaceutiquement acceptables.

31. 1 - (4 - chlorobenzhydryl) - 4 - (2,4,6 - triméthylphénylcarbamoylméthyl)pipérazine et ses sels pharmaceutiquement acceptables.

32. 1 - [bis(4 - fluorophényl)méthyl] - 4 - [(4 - méthoxyphényl)carbamoylméthyl] - 2,5 - diméthylpipérazine et ses sels pharmaceutiquement acceptables.

33. 1 - [bis(4 - fluorophényl)méthyl] - 4 - [(2,4,6 - triméthylphényl)carbamoylméthyl] - 3 - méthylpipérazine et ses sels pharmaceutiquement acceptables.

34. 1 - [bis(4 - fluorophényl)méthyl] - 4 - [(3 - fluorophényl)carbamoylméthyl] - 3,3 - diméthylpipérazine et ses sels pharmaceutiquement acceptables.

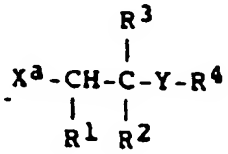
35. 1 - [bis(4 - fluorophényl)méthyl] - 4 - [1 - (1 - adamantylcarbamoyl)éthyl]homopipérazine et ses sels pharmaceutiquement acceptables.

36. Composition pharmaceutique comprenant un inhibiteur de l'entrée du calcium en mélange avec un véhicule ou diluant pharmaceutiquement acceptables, dans laquelle ledit inhibiteur de l'entrée du calcium est au moins un composé selon l'une quelconque des revendications précédentes.

37. Procédé pour préparer un composé selon l'une quelconque des revendications 1 à 35, qui comprend la réaction d'un composé de formule (IV) :

A - M - H (IV)

(dans laquelle A et M sont définis comme dans la revendication 1) ou un dérivé actif de celui - ci avec un composé de formule (V) :



(V)

(dans laquelle R^1, R^2, R^3 et R^4 sont définis comme dans la revendication 1, et X^a représente un atome d'halogène, un groupe acyloxy carboxylique ou un groupe sulfonyloxy) et, facultativement, lorsque R^4 et/ou R^5 représentent un atome d'hydrogène, la réaction du composé obtenu avec un réactif approprié, pour introduire un groupe alkyle, aryle, aralkyle, hétérocyclique aromatique ou alcényle sur l'atome d'azote figurant dans la définition de $-Y-R^4$.

38. Utilisation pour la préparation d'un médicament pour le traitement de troubles vasculaires d'au moins un composé selon l'une quelconque des revendications 1 à 35.

39. Utilisation pour la préparation d'un médicament pour le traitement des troubles ischémiques d'au moins un composé selon l'une quelconque des revendications 1 à 35.

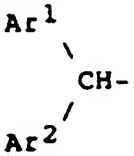
40. Utilisation pour la préparation d'un médicament pour protéger un animal contre les effets nuisibles de l'anoxie d'au moins un composé selon l'une quelconque des revendications 1 à 35.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour préparer un composés de formule (I) :

A - M - B (I)

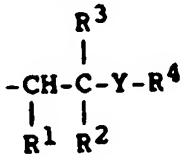
[dans laquelle :
M représente un groupe hétérocyclique saturé ayant de 5 à 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou étant substitué sur des atomes de carbone quelconques avec au moins un substituant alkyle en $C_1 - C_6$ et/ou oxo ;
A représente un substituant sur l'un desdits atomes d'azote et a pour formule (II) :



(II)

dans laquelle Ar^1 représente un groupe phényle ayant un substituant X^1 et Ar^2 représente un groupe

phényle ayant un substituant X^2, où un de X^1 et de X^2 représente un atome d'hydrogène ou un atome d'halogène et l'autre de X^1 et de X^2 représente un atome d'halogène ;
B représente un substituant sur l'autre atome d'azote et a pour formule (III) :



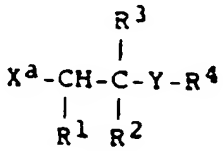
(III)

dans laquelle R^1 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ;
R^2 et R^3 représentent ensemble un groupe oxo ;
Y représente un groupe de formule $-NR^5-$;
R^4 et R^5 sont semblables ou différents et représentent chacun un atome d'hydrogène, un groupe aryle, un groupe alkyle en C_1-C_6, un groupe alkyle en C_1-C_6 substitué ayant au moins un des substituants (a), un groupe cycloalkyle en C_3-C_{10}, un groupe hétérocyclique aromatique ou un groupe alcényle en C_2-C_6, ou $-Y-R^4$ conjointement représente un groupe hétérocyclique monocyclique ou un groupe hétérocyclique monocyclique auquel un cycle aromatique est condensé ;
lesdits groupes cycloalkyle sont définis comme étant non substitués ou ont au moins un substituant alkyle en C_1-C_4 et sont saturés ou ont au moins une double liaison carbone-carbone à insaturation éthylénique ;
lesdits groupes aryle sont définis comme des groupes aromatiques carbocycliques ayant de 6 à 14 atomes de carbone formant le cycle et sont non substitués ou ont au moins un des substituants (b) et/ou des substituants (c) ;
lesdits groupes hétérocycliques aromatiques sont définis comme ayant un cycle hétérocylique contenant 5 à 7 atomes formant le cycle dont 1 à 3 sont des hétéroatomes d'azote et/ou d'oxygène et/ou de soufre ou ont ledit cycle hétérocylique condensé à un cycle hétérocyclique ou carbocyclique ayant de 5 à 7 atomes formant le cycle, lesdits groupes hétérocycliques aromatiques étant non substitués ou ayant au moins un des substituants (b) et/ou des substituants (d) ;
lesdits groupes hétérocycliques monocycliques sont définis comme ayant 4 à 12 atomes formant le cycle dont 1 à 5 sont des hétéroatomes d'azote et/ou d'oxygène et/ou de soufre, lesdits groupes hétérocycliques monocycliques étant non substitués ou ayant au moins un des substituants (b) et/ou des substituants (d) ;
lesdits groupes hétérocycliques monocycliques ayant un cycle aromatique qui leur est condensé sont définis comme ayant undit groupe hétérocyclique monocyclique et un cycle aromatique condensé qui est un cycle hétérocyclique ou carbocyclique ayant de 6 à 12 atomes formant le cycle ; lesdits groupes hétérocycliques monocycliques et lesdits cycles aromatiques étant non substitués ou ayant au moins un des substituants (b) et/ou des substituants (d) ;
substituants (a) :
atomes d'halogène, groupes aryle, groupes hydroxy, groupes alcoxy en C_1-C_6, groupes nitro, groupes cyano, groupes hétérocycliques, groupes carboxy, groupes alcoxycarbonyle en C_2-C_7, groupes aryloxycarbonyle, groupes aralkyloxycarbonyle dont la partie alkyle est en C_1-C_4, groupes acyle carboxyliques aliphatiques en C_1-C_7, groupes acyle carboxyliques aromatiques et groupes acyle carboxyliques hétérocycliques ;
substituants (b) :
groupes alkyle en C_1-C_4, groupes nitro, groupes cyano, groupes hydroxy, groupes alcoxy en C_1-C_4, groupes aryloxy, groupes aralkyloxy dont la partie alkyle est en C_1-C_4, groupes acyloxy carboxyliques aliphatiques en C_1-C_7, groupes alkylthio en C_1-C_4, groupes arylthio, groupes aralkylthio dont la partie alkyle est en C_1-C_4, groupes alkylsulfinyle en C_1-C_4, groupes alkylsulfonyle en C_1-C_4, groupes arylsulfinyle, groupes arylsulfonyle, groupes acylamino carboxyliques aliphatiques en C_1-C_7, groupes acylamino carboxyliques aromatiques, groupes alcoxycarbonylamino en C_2-C_7, groupes aralkyloxycarbonylamino dont la partie alkyle est en C_1-C_4, groupes alcoxycarbonyle en C_2-C_7, groupes aryloxycarbonyle, groupes aralkyloxycarbonyle dont la partie alkyle est en C_1-C_4, groupes acyle carboxyliques aliphatiques en C_1-C_7, groupes acyle carboxyliques aromatiques, groupes acyle carboxyliques hétérocycliques, groupes carbamoyle, groupes alkylcarbamoyle dont la partie alkyle est en C_1-C_4, groupes dialkylcarbamoyle dont chaque partie alkyle est en C_1-C_4, groupes thiocarbamoyle, groupes alkyl(thiocarbamoyle) dont la partie alkyle est en C_1-C_4, groupes dialkyl-(thiocarbamoyle) dont chaque partie alkyle est en C_1-C_4, groupes uréido, groupes alkyluréido dont la

partie alkyle est en C_1-C_4, groupes dialkyluréido dont chaque partie alkyle est en C_1-C_4, groupes thio-uréido, groupes alkyl(thio-uréido) dont la partie alkyle est en C_1-C_4, groupes dialkyl(thio-uréido) dont chaque partie alkyle est en C_1-C_4, groupes cycloakyle en C_3-C_8, groupes cycloalcénylе en C_5-C_8, groupes aryle, groupes hétérocycliques, atomes d' halogène, groupes alkyle en C_1-C_6 ayant au moins un substituant halogène, groupes mercapto, groupes amino, groupes alkylamino en C_1-C_4, groupes dialkylamino dont chaque partie alkyle est en C_1-C_4, groupes carboxy, groupes (hydroxyalkyl en C_1-C_4)amino, groupes di(hydroxyalkyl en C_1-C_4)amino, groupes guanidino et groupes guanidino ayant au moins un substituant alkyle en C_1-C_4 ;
avec pour réserves que
tout groupe cycloalkyle présent dans les substituants possibles est conforme à la définition de : "lesdits groupes cycloalkyle" ;
tout groupe aryle présent dans les substituants possibles est conforme à la définition de : "lesdits groupes aryle" ;
tout groupe hétérocyclique présent dans les substituants possibles est conforme aux définitions de : "lesdits groupes hétérocycliques aromatiques", "lesdits groupes hétérocycliques monocycliques" ou "lesdits groupes hétérocycliques monocycliques ayant un cycle aromatique qui leur est condensé" ;
lorsqu'un substituant (a) ou (b) représente un groupe qui lui-même peut être substitué par un autre substituant qui est un substituant (a) ou (b), alors cet autre substituant n'est pas lui-même substitué ;
substituants (c) :
groupes alkylènedioxy ayant de 1 à 6 atomes de carbone ;
substituants (d) :
atomes d'oxygène ;
et ses sels pharmaceutiquement acceptables
à l'exclusion des composés dans lesquels M représente un groupe pipérazine non substitué, A répond à la formule (II) dans laquelle Ar^1 est un groupe 4-chlorophényle et Ar^2 est un groupe phényle et B répond à la formule (III) dans laquelle R^1, R^4 et R^5 sont un atome d'hydrogène et R^2, R^3 et Y sont comme définis]
lequel procédé comprend la réaction d'un composé de formule (IV) :

$$A-M-H \quad (IV)$$

(dans laquelle A et M sont définis comme ci-dessus) ou un dérivé actif de celui-ci avec un composé de formule (V) :



(V)

(dans laquelle R^1, R^2, R^3 et R^4 sont définis comme ci-dessus, et X^a représente un atome d'halogène, un groupe acyloxy carboxylique ou un groupe sulfonyloxy) et, facultativement, lorsque R^4 et/ou R^5 représentent un atome d'hydrogène, la réaction du composé obtenu avec un réactif approprié, pour introduire un groupe alkyle, aryle, aralkyle, hétérocyclique aromatique ou alcényle sur l'atome d'azote figurant dans la définition de $-Y-R^4$.

2. Procédé selon la revendication 1, où M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, de 1 à 4 substituants alkyle en C_1-C_6 et/ou oxo.

3. Procédé selon la revendication 1, où M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en C_1-C_4 et/ou oxo.

4. Procédé selon la revendication 1, où M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 à 4 substituants alkyle en C_1-C_4 et/ou oxo ;

5. Procédé selon la revendication 1, où M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;

6. Procédé selon la revendication 1, où au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène dans sa position 4.

7. Procédé selon la revendication 1, où R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$.

8. Procédé selon la revendication 1, où R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_2$.

9. Procédé selon la revendication 1, où R^1 représente un atome d'hydrogène ou un groupe méthyle.

10. Procédé selon l'une quelconque des revendications précédentes, où un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe aryle carbocyclique en $C_6 - C_{10}$, un groupe aralkyle dont la partie aryle est en $C_6 - C_{10}$, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe aryle ou aralkyle ayant au moins un des substituants (b) et/ou (c).

11. Procédé selon l'une quelconque des revendications précédentes, où un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b) et/ou (c).

12. Procédé selon l'une quelconque des revendications précédentes, où X^1 et X^2 représentent tous deux des atomes de fluor.

13. Procédé selon l'une quelconque des revendications 1 à 12, où un de X^1 et de X^2 représente un atome de chlore et l'autre représente un atome d'hydrogène.

14. Procédé selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont deux sont des atomes d'azote, ledit groupe étant non substitué ou ayant sur des atomes de carbone quelconques de 1 à 4 substituants choisis parmi les groupes alkyle en $C_1 - C_6$ et les groupes oxo ; et
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_6$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe aryle carbocyclique en $C_6 - C_{10}$, un groupe aralkyle dont la partie aryle est en $C_6 - C_{10}$, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe aryle ou aralkyle ayant au moins un des substituants (b) et/ou (c).

15. Procédé selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont deux sont des atomes d'azote, ledit groupe étant non substitué ou ayant sur un de ses atomes de carbone de 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe aryle carbocyclique en $C_6 - C_{10}$, un groupe aralkyle dont la partie aryle est en $C_6 - C_{10}$, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe aryle ou aralkyle ayant au moins un des substituants (b) et/ou (c).

16. Procédé selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des

atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b) et/ou (c).

17. Procédé selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, un ou deux substituants alkyle en $C_3 - C_4$ et/ou oxo ;
X^1 et X^2 représentent tous deux des atomes de fluor ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

18. Procédé selon la revendication 1, où :
M représente un groupe hétérocyclique saturé ayant 6 ou 7 atomes formant le cycle dont 2 sont des atomes d'azote, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
un de X^1 et de X^2 représente un atome de chlore et l'autre représente un atome d'hydrogène ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

19. Procédé selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_6$; R^2 et R^3 ensemble représentent un groupe oxo ; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

20. Procédé selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 à 4 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

21. Procédé selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
au moins un de Ar^1 et de Ar^2 représente un groupe phényle ayant un substituant halogène sur sa position 4 ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle

en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

22. Procédé selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
X^1 et X^2 représentent tous deux des atomes de fluor ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

23. Procédé selon la revendication 1, où :
M représente un groupe pipérazinyle ou un groupe homopipérazinyle, ledit groupe étant non substitué ou ayant, sur des atomes de carbone quelconques, 1 ou 2 substituants alkyle en $C_1 - C_4$ et/ou oxo ;
un de X^1 et de X^2 représente un atome de chlore et l'autre représente un atome d'hydrogène ;
R^1 représente un atome d'hydrogène ou un groupe alkyle en $C_1 - C_4$; et
un de R^4 et de R^5 représente un atome d'hydrogène, un groupe alkyle en $C_1 - C_4$ ou un groupe alcényle en $C_2 - C_4$ et l'autre représente un groupe phényle, un groupe benzyle, un groupe cycloalkyle en $C_6 - C_{10}$ ou ledit groupe phényle ou benzyle ayant au moins un des substituants (b).

24. Procédé selon la revendication 1, dans lequel les réactifs et les conditions de réaction sont choisis pour préparer les :
1 - [bis(4 - fluorophényl)méthyl] - 4 - (2,4,6 - triméthylphénylcarbamoylméthyl)pipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - (1,1 - diméthylbenzylcarbamoylméthyl)pipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - (3 - fluorophénylcarbamoylméthyl)pipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [N - allyl - N - (3 - fluorophényl)carbamoylméthyl]pipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [1 - (1,2,3,4 - tétrahydroquinoléine - 1 - carbonyl)éthyl]pipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [1 - (3 - fluorophénylcarbamoyl)éthyl]pipérazine ;
1 - (4 - chlorobenzhydryl) - 4 - (4 - méthoxyphénylcarbamoylméthyl)pipérazine ;
1 - (4 - chlorobenzhydryl) - 4 - (2,4,6 - triméthylphénylcarbamoylméthyl)pipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [(4 - méthoxyphényl)carbamoylméthyl] - 2,5 - diméthylpipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [(2,4,6 - triméthylphényl)carbamoylméthyl] - 3 - méthylpipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [(3 - fluorophényl)carbamoylméthyl] - 3,3 - diméthylpipérazine ;
1 - [bis(4 - fluorophényl)méthyl] - 4 - [1 - (1 - adamantylcarbamoyl)éthyl]homopipérazine ;
ou un de leurs sels pharmaceutiquement acceptables.

25. Utilisation pour la préparation d'un médicament pour le traitement des troubles vasculaires d'au moins un composé de formule (I) défini comme dans la revendication 1 ou d'un sel pharmaceutiquement acceptable de celui - ci.

26. Utilisation pour la préparation d'un médicament pour le traitement des troubles ischémiques d'au moins un composé de formule (I) défini comme dans la revendication 1 ou d'un sel pharmaceutiquement acceptable de celui - ci.

27. Utilisation pour la préparation d'un médicament pour protéger un animal contre les effets nuisibles de l'anoxie d'au moins un composé de formule (I) défini comme dans la revendication 1 ou d'un sel pharmaceutiquement acceptable de celui - ci.